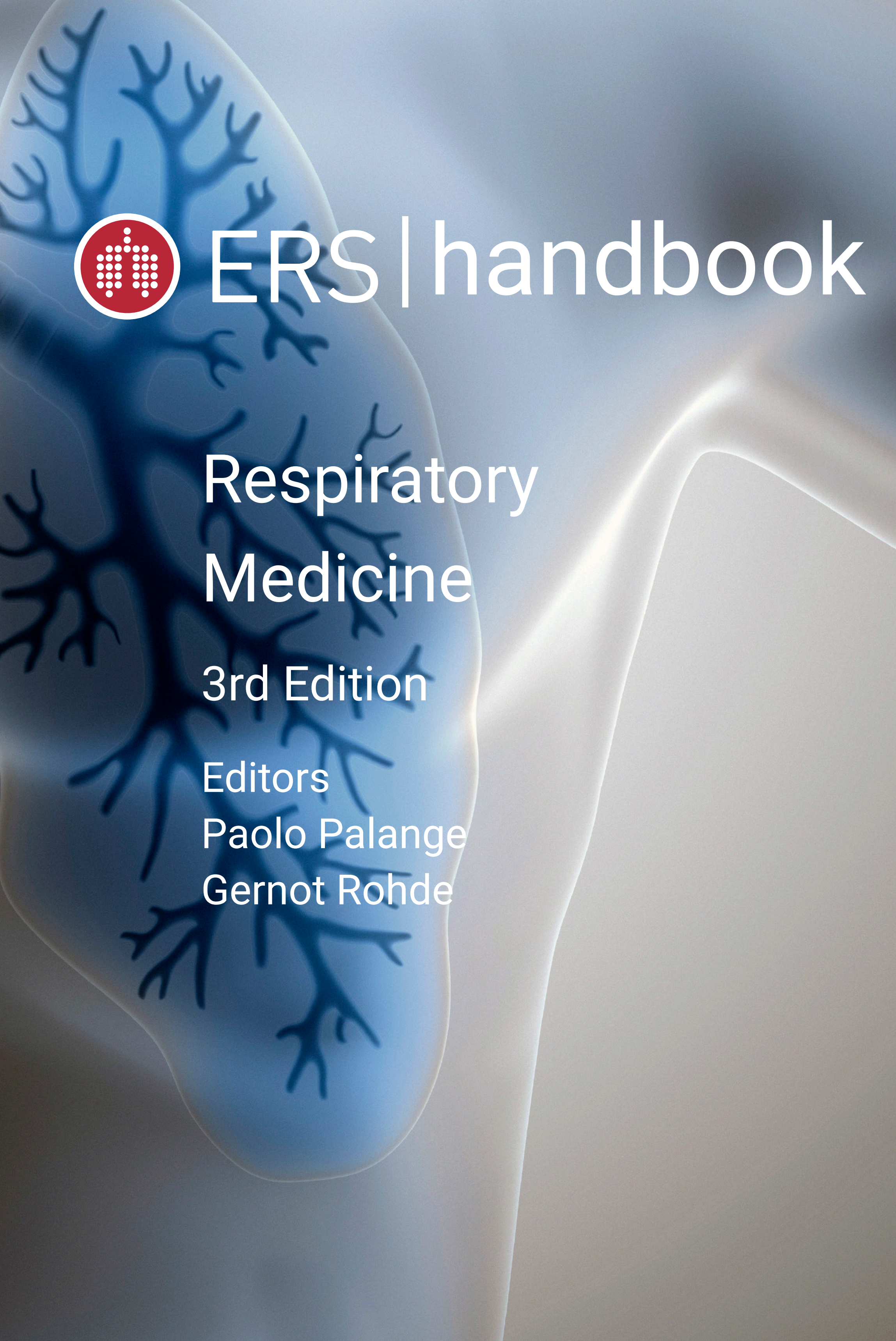


ERS | handbook

Respiratory Medicine

3rd Edition

Editors
Paolo Palange
Gernot Rohde

ERS | handbook

Respiratory Medicine

3rd Edition

Editors
Paolo Palange
Gernot Rohde

PUBLISHED BY
THE EUROPEAN RESPIRATORY SOCIETY

CHIEF EDITORS
Paolo Palange (Rome, Italy)
Gerhot Rohde (Frankfurt, Germany)

ERS STAFF
Caroline Ashford-Bentley, Alice Bartlett, Matt Broadhead, Alyson Cann,
Sarah Cleveland, Rachel Gozzard, Jonathan Hansen, Catherine Pumphrey,
Elin Reeves, Claire Marchant, Ben Watson

© 2019 European Respiratory Society

Design by Claire Marchant, ERS
Typeset in India by Nova Techset
Indexed by Merrall-Ross International, UK
Printed in UK by Latimer Trend & Co. Ltd, UK

All material is copyright to the European Respiratory Society.
It may not be reproduced in any way including electronically without the express permission of the society.

CONTACT, PERMISSIONS AND SALES REQUESTS:
European Respiratory Society, 442 Glossop Road, Sheffield, S10 2PX, UK
Tel: +44 114 2672860 Fax: +44 114 2665064 e-mail: books@ersnet.org

ISBN 978-1-84984-079-8

FSC
www.fsc.org
MIX
Paper from
responsible sources
FSC® C013436

Table of contents

Contributors **xiv**
Preface **xxix**
List of abbreviations **xxx**

1 – Structure and function of the respiratory system

Anatomy of the respiratory system 1
Pallav L. Shah

Cytology of the lung 7
Venerino Poletti, Giovanni Poletti and Marco Chilosi

Immunology and defence mechanisms 20
Antonino Di Stefano and Bruno Balbi

2 – Physiology and pulmonary function testing

Respiratory physiology 28
Susan A. Ward

Control of ventilation 41
Brian J. Whipp and Susan A. Ward

Respiratory mechanics 48
Daniel Navajas and Ramon Farré

Gas transfer 54
J. Mike Hughes

Arterial blood gas assessment 60
Paolo Palange and Alessandro Ferrazza

Exercise testing 70
Paolo Palange and Paolo Onorati

Bronchial provocation testing 77
Frans de Jongh

Static and dynamic lung volumes 83
Riccardo Pellegrino, Andrea Antonelli and Frans de Jongh

Assessment for anaesthesia/surgery 90
Macé M. Schuurmans, Carolin Steinack and Markus Solèr

3 – Diagnostic approach

Dyspnoea 97
Pierantonio Laveneziana

Chest pain 108
Matthew Hind

Cough 110
Alyn H. Morice

Physical examination 117
Martyn R. Partridge

4 – Diagnostic procedures

Bronchoscopy 124
Pallav L. Shah

Interventional pulmonology 132
Hervé Dutau and David Breen

Bronchoalveolar lavage 138
Ulrich Costabel, Francesco Bonella and Josune Guzman

Medical thoracoscopy/pleuroscopy 145
Philippe Astoul

Thoracentesis 151
Emilio Canalis

Chest radiography and fluoroscopy 154
Walter De Wever

Transthoracic ultrasound 160
Jane A. Shaw, Florian von Groote-Bidlingmaier and Coenraad F.N. Koegelenberg

Lung CT and MRI 169
Johny A. Verschakelen

HRCT of the chest 175
Johny A. Verschakelen

Nuclear medicine of the lung 181
Antonio Palla and Duccio Volterrani

Sputum and exhaled breath analysis 187
Patrizia Pignatti, Dina Visca, Elisiana Carpagnano, Francesca Cherubino and Antonio Spanevello

Microbiology testing and interpretation 194
Margareta Ieven and Veerle Matheeussen

Laboratory diagnosis of mycobacterial infections 201
Claudio Piersimoni

Biopsy 207
Stefano Gasparini

5 – General principles of treatment modalities and prevention measures

Inhaled drug therapy 210
Omar S. Usmani

Systemic pharmacotherapy 215
Mario Cazzola, Paola Rogliani and Maria Gabriella Matera

Allergen-specific immunotherapy 223
Christian Taube

Immunotherapies in lung cancer 227
Niels Reinmuth

Respiratory physiotherapy 232
Thierry Troosters and Julia Bott

Pulmonary rehabilitation 239
Thierry Troosters, Wim Janssens, Daniel Langer and Heleen Demeyer

Palliative care 249
Sylvia Hartl

Oxygen therapy 253
Anita K. Simonds

Smoking-related diseases 257
Linnea Hedman

Treatment of tobacco dependence 261
Charlotta Pisinger

Long-term ventilation 266
Anita K. Simonds

Pleural infection and lung abscess 273
Amelia Clive, William Falconer, Clare Hooper and Nick Maskell

Endoscopic lung volume reduction 282
Ralf Eberhardt and Maren Schuhmann

Lung transplantation 288
Geert M. Verleden

6 – Respiratory emergencies

Respiratory emergencies 293
Maxens Decavèle, Suela Demiri and Alexandre Demoule

Lung injury and acute respiratory distress syndrome 299
Bernd Schönhofer and Christian Karagiannidis

7 – Airway diseases

Upper airway disease 304
Claus Bachert

Asthma 308
Bianca Beghé, Leonardo M. Fabbri and Paul M. O’Byrne

Bronchitis 320
Koliarne Tong and Peter Wark

COPD and emphysema 324
Emma Burke and John R. Hurst

Exacerbations of COPD 332
Marc Miravitlles

Extrapulmonary effects of COPD 339
Yvonne Nussbaumer-Ochsner and Klaus F. Rabe

Pharmacology of asthma and COPD 344
Peter J. Barnes

Bronchiectasis 353
James D. Chalmers

Rare airway diseases 358
Mouhamad Nasser and Vincent Cottin

Congenital airway disease 364
Ernst Eber

8 – Respiratory infections

Upper respiratory tract infections 372
Gernot Rohde

Pneumonia 377
Gernot Rohde and Mark Woodhead

Hospital-acquired pneumonia 383
Francesco Blasi, Andrea Gramegna and Marta Di Pasquale

Pneumonia in the immunocompromised host 388
Santiago Ewig

Influenza, pandemics and SARS 393
Wei Shen Lim

Opportunistic infections in the immunocompromised host 400
Thomas Fuehner, Diana Ernst, Mark Greer, Jens Gottlieb and Tobias Welte

Aspiration pneumonitis 411
John MacSharry and Desmond M. Murphy

9 – Mycobacterial diseases

Pulmonary tuberculosis 416
Giovanni Sotgiu and Giovanni Battista Migliori

Tuberculosis in immunocompromised patients 429
Martina Sester

Extrapulmonary tuberculosis 433
Demosthenes Bouros and Argyrios Tzouvelekis

Latent tuberculosis 438
Jean-Pierre Zellweger

Nontuberculous mycobacterial disease 442
Claudio Piersimoni

10 – Thoracic tumours

Pathology and molecular biology of lung cancer 447
Verena Tischler, Sylvie Lantuejoul, Lénaïg Mescam-Mancini,
Barbara Burroni and Anne McLeer-Florin

Lung cancer: diagnosis and staging 453
Johan Vansteenkiste, Griet Deslypere and Dorothee Gullentops

Chemotherapy and molecular biological therapy 463
Amanda Tufman and Rudolf M. Huber

Surgical treatment for lung cancer 472
Gilbert Massard, Anne Olland and Pierre-Emmanuel Falcoz

Radiotherapy for lung cancer 481
Luigi Moretti and Paul Van Houtte

Other lung tumours 490
Andrew Cheng and Matthew Evison

Metastatic tumours 495
Elisabeth Quoix

Pulmonary nodules 501
David R. Baldwin

Pleural and chest wall tumours 506
Arnaud Scherpereel

Mediastinal tumours 514
Lawek Berzenji, Laurens Carp, Jeroen M. Hendriks, Patrick Lauwers and Paul E. Van Schil

11 – Sleep and control of breathing disorders

Obstructive sleep apnoea–hypopnoea syndrome 522
Wilfried De Backer

Central sleep apnoea 529
Konrad E. Bloch and Thomas Brack

Hypoventilation syndromes 535
Andrea Aliverti

12 – Respiratory failure

Respiratory failure 541
Nicolino Ambrosino and Fabio Guarracino

NIV in acute respiratory failure 546
Anita K. Simonds

13 – Diffuse parenchymal lung diseases

Idiopathic pulmonary fibrosis 553
Pier-Valerio Mari, Athol Wells and Luca Richeldi

Hypersensitivity pneumonitis 557
Torben Sigsgaard and Anna Rask-Andersen

Sarcoidosis 563
Ulrich Costabel

Idiopathic interstitial pneumonias 568
Marina Aiello, Alberto Fantin, Panayota Tzani, Sara Chiesa and Dario Olivieri

Adult pulmonary Langerhans cell histiocytosis 581
Vincent Cottin, Mouhamad Nasser, Claudia Valenzuela and Romain Lazor

Lymphangioleiomyomatosis 585
Vincent Cottin, Romain Lazor, Claudia Valenzuela and Paolo Spagnolo

Pulmonary alveolar proteinosis 589
Paolo Palange and Francesco Vaccaro

Amyloidosis 592
Helen J. Lachmann

Drug-induced and iatrogenic respiratory disease 595
Philippe Camus and Philippe Bonniaud

Radiation-induced lung disease 612
Peter van Luijk and Robert P. Coppes

Eosinophilic diseases 615
Claire McBrien and Andrew Menzies-Gow

14 – Pulmonary vascular diseases

Pulmonary embolism 620
Mariaelena Occhipinti and Massimo Pistolesi

Pulmonary hypertension 628
Jason Weatherald and Marc Humbert

Pulmonary vasculitis 637
George A. Margaritopoulos and Athol U. Wells

Arteriovenous malformations 646
Camilla Poggi, Sara Mantovani, Daniele Diso, Jacopo Vannucci, Federico Venuta and Marco Anile

15 – Diseases of the chest wall and respiratory muscles

Chest wall disorders 649
Pierre-Emmanuel Falcoz, Nicola Santelmo, Anne Olland and Gilbert Massard

Neuromuscular disorders and the diaphragm 653
Michael I. Polkey and Anita K. Simonds

16 – Pleural and mediastinal diseases

Pleural effusion 660
Robert Loddenkemper and Julius Janssen

Pneumothorax and pneumomediastinum 666
Julius Janssen

Mediastinitis 671
Pierre-Emmanuel Falcoz, Nicola Santelmo, Anne Olland and
Gilbert Massard

17 – Respiratory consequences of systemic/extrapulmonary conditions

Pulmonary diseases in primary immunodeficiency syndromes 675
Federica Pulvirenti, Cinzia Milito and Isabella Quinti

HIV-related disease 681
Marc C.I. Lipman and Robert F. Miller

Cardiac disease 692
Enrico Clini, Sara Roversi, Bianca Beghé and Leonardo M. Fabbri

Gastrointestinal and liver disease 701
Harald Farnik and Gernot Rohde

Haematological diseases 707
Anna Paola Iori

Obesity 716
Frits M.E. Franssen

Connective tissue diseases 722
Edoardo Rosato

18 - Genetic disorders

Cystic fibrosis 727
Marcello Di Paolo, Joseph Stuart Elborn and Paolo Palange

Primary ciliary dyskinesia 740
Jane S. Lucas and Woolf T. Walker

α_1-antitrypsin deficiency 744
Robert A. Stockley

19 - Occupational diseases

Occupational diseases 748
Johanna Feary and Paul Cullinan

20 - Epidemiology, environment and lifestyle

Measuring the occurrence and causation of respiratory diseases 753
Isabella Annesi-Maesano and Riccardo Pistelli

Indoor and outdoor pollution 771
Giovanni Viegi, Marzia Simoni, Sara Maio and Sandra Baldacci

High altitude and diving-related diseases 779
Yvonne Nussbaumer and Konrad E. Bloch

Contributors

Chief Editors

Paolo Palange
Dept of Public Health and
Infectious Diseases
Sapienza University of Rome
Rome, Italy
paolo.palange@uniroma1.it

Gernot Rohde
Medical Clinic I
Dept of Respiratory Medicine
J.W. Goethe University Hospital
Frankfurt, Germany
gernot.rohde@kgu.de

Authors

Marina Aiello
Respiratory Disease and Lung Function
Unit, Dept of Medicine and Surgery,
University of Parma
Parma, Italy
marina.aiello@unipr.it

Andrea Aliverti
Dipartimento di Elettronica,
Informazione e Bioingegneria
Milan, Italy
andrea.aliverti@polimi.it

Nicolino Ambrosino
Istituto di Montescano
Montescano, Italy
nico.ambrosino@gmail.com

Marco Anile
Dept of Thoracic Surgery, Sapienza
University of Rome
Rome, Italy
marco.anile@uniroma1.it

Isabella Annesi-Maesano
iPLESP – EPAR Dept, INSERM and
Sorbonne University Medical School
Saint-Antoine
Paris, France
isabella.annesi-maesano@inserm.fr

Andrea Antonelli
ASO S. Croce e Carle – Fisiopatologia
Respiratoria
Cuneo, Italy
andrea-antonelli@tiscali.it

Philippe Astoul
Dept of Thoracic Oncology,
Pleural Diseases and Interventional
Pulmonology, Hôpital Nord
Marseille, France
pastoul@ap-hm.fr

Claus Bachert
Ghent University and Ghent University
Hospital
Ghent, Belgium
Claus.Bachert@ugent.be

Bruno Balbi
Istituti Clinici Scientifici Maugeri, IRCCS,
SpA Società Benefit,
Divisione di Pneumologia e Laboratorio
di Citoimmunopatologia dell'Apparato
Cardio Respiratorio
Veruno, Italy
bruno.balbi@icsmaugeri.it

Sandra Baldacci
Clinical Physiology Institute, CNR
Pisa, Italy
baldas@ifc.cnr.it

David R. Baldwin
Nottingham University Hospitals and
University of Nottingham Respiratory
Medicine Unit, David Evans Centre
Nottingham, UK
David.baldwin@nuh.nhs.uk

Peter J. Barnes
National Heart and Lung institute,
Imperial College
London, UK
p.j.barnes@imperial.ac.uk

Bianca Beghé
Section of Respiratory Diseases, Dept
of Medical and Surgical Sciences,
University of Modena and Reggio Emilia
Modena, Italy
bianca.beghe@unimore.it

Lawek Berzenji
Thoracic and Vascular Surgery, Antwerp
University Hospital,
Antwerp, Belgium
Lawek.Berzenji@uantwerpen.be

Francesco Blasi
Dept of Pathophysiology and
Transplantation, Università degli Studi
di Milano, and Internal Medicine Dept,
Respiratory Unit and Adult Cystic
Fibrosis Center, Fondazione IRCCS Cà
Granda Ospedale Maggiore Policlinico
Milan, Italy
francesco.blasi@unimi.it

Konrad E. Bloch
University Hospital Zurich, Dept of
Respiratory Medicine
Zurich, Switzerland
konrad.bloch@usz.ch

Francesco Bonella
Dept of Pneumology, Ruhrlandklinik,
University Hospital
Essen, Germany
Francesco.Bonella@ruhrlandklinik.uk-essen.de

Philippe Bonniaud
CHU Bocage, Service de Pneumologie
Dijon, France
philippe.bonniaud@chu-dijon.fr

Julia Bott
Kent Surrey Sussex Academic Health
Science Network
Crawley, UK
juliabott@aol.com

Demosthenes Bouros
Interstitial Lung Diseases Unit, Medical
School, National and Kapodistrian
University of Athens, Hospital for
Diseases of the CHEST ‘SOTIRIA’
Athens, Greece
dbouros@med.uoa.gr

Thomas Brack
Kantonsspital
Glarus, Switzerland
thomas.brack@ksgl.ch

David Breen
Interventional Respiratory Unit, Dept of
Respiratory Medicine, Galway University
Hospitals
Galway, Ireland
david.breen@hse.ie

Emma Burke
UCL Respiratory, University College
London
London, UK
emma.burke6@nhs.net

Barbara Burroni
Département de Pathologie,
Pôle de Biologie et de Pathologie,
Centre Hospitalier Universitaire A.
Michallon, INSERM U 823 – Institut A.
Bonniot, Université J. Fourier
Grenoble, France
BBurroni@chu-grenble.fr

Philippe Camus
CHU Dijon
Dijon, France
phil.camus@me.com

Emilio Canalis
Universitat Rovira i Virgili, Dept of
Medicine and Surgery
Tarragona, Spain
emilio.canalis@gmail.com

Laurens Carp
Dept of Nuclear Medicine,
Antwerp University Hospital,
Antwerp, Belgium
laurens.carp@uza.be

Elisiana Carpagnano
Dept of Medical and Surgical
Sciences, University of Foggia, Italy
giovannaelisiana.carpagnano@unifg.it

Mario Cazzola
Dept of Experimental Medicine,
University of Rome Tor Vergata
Rome, Italy
mario.cazzola@uniroma2.it

James D. Chalmers
Scottish Centre for Respiratory
Research, University of Dundee
Dundee, UK
jchalmers@dundee.ac.uk

Andrew Cheng
North West Deanery
Manchester, UK
andrew.cheng@nhs.net

Francesca Cherubino
Division of Pulmonary Rehabilitation,
Istituti Clinici Scientifici Maugeri, IRCCS
Tradate,
Tradate, Italy
francesca.cherubino@icsmaugeri.it

Sara Chiesa
Respiratory Disease and Lung
Function Unit, Dept of Medicine and
Surgery, University of Parma
Parma, Italy
sara.chiesa@hotmail.it

Marco Chilosi
Dept of Anatomic Pathology, University
of Verona
Verona, Italy
marco.chilosi@univr.it

Amelia Clive
Academic Respiratory Unit, University
of Bristol
Bristol, UK
Amelia.Clive@nbt.nhs.uk

Enrico Clini
University of Modena Reggio Emilia -
Medical and Surgical Sciences
Modena, Italy
enrico.clini@unimore.it

Ulrich Costabel
Dept of Pneumology, Ruhrlandklinik,
University Hospital
Essen, Germany
ulrich.costabel@ruhrlandklinik.uk-essen.de

Vincent Cottin
Hospices Civils de Lyon, Dept of
Respiratory Medicine, National
Reference Center for Rare Pulmonary
Diseases, and Claude Bernard Lyon 1
University, University of Lyon, INRA,
UMR754
Lyon, France
vincent.cottin@chu-lyon.fr

Robert P. Coppes
University of Groningen, University
Medical Center Groningen
Groningen, The Netherlands
r.p.coppes@umcg.nl

Paul Cullinan
Royal Brompton Hospital
London, UK
p.cullinan@imperial.ac.uk

Wilfried De Backer
Dept of Pulmonary Medicine, University of Antwerp
Antwerp, Belgium
wilfried.debacker@uantwerpen.be

Maxens Decavèle
Sorbonne Université, INSERM, UMRS_1158 Neurophysiologie respiratoire expérimentale et clinique, and AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie, Médecine Intensive et Réanimation du Département ‘R3S’
Paris, France
maxencesar@hotmail.fr

Frans de Jongh
Pulmonology, Medisch Spectrum Twente
Enschede, The Netherlands
f.dejongh@mst.nl

Heleen Demeyer
Dept of Rehabilitation Sciences, KU Leuven
Leuven, Belgium
heleen.demeyer@kuleuven.be

Suela Demiri
Sorbonne Université, INSERM, UMRS_1158 Neurophysiologie respiratoire expérimentale et clinique, and AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie, Médecine Intensive et Réanimation du Département ‘R3S’
Paris, France
demiri.suela@gmail.com

Alexandre Demoule
Sorbonne Université, INSERM, UMRS_1158 Neurophysiologie respiratoire expérimentale et clinique, and AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie, Médecine Intensive et Réanimation du Département ‘R3S’
Paris, France
alexandre.demoule@aphp.fr

Griet Deslypere
Respiratory Oncology Unit, Dept of Respiratory Medicine, University Hospital KU Leuven
Leuven, Belgium
griet.deslypere@uzleuven.be

Walter De Wever
Dept of Radiology, University Hospital
Leuven, Belgium
walter.dewever@uzleuven.be

Marcello Di Paolo
Dept of Public Health and Infectious Diseases, ‘Sapienza’ University of Rome
Rome, Italy
marcello.dipaolo@uniroma1.it

Marta Di Pasquale
Dept of Pathophysiology and Transplantation, Università degli Studi di Milano, and Internal
Medicine Dept, Respiratory Unit and Adult Cystic, Fibrosis Center, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico
Milan, Italy
marta.dipasquale@gmail.com

Daniele Diso
Dept of Thoracic Surgery, Sapienza University of Rome
Rome, Italy
daniele.diso@uniroma1.it

Hervé Dutau
Interventional Pulmonology
Department, North University Hospital,
Aix-Marseille University,
Marseille, France
hdutau@ap-hm.fr

Ernst Eber
Division of Paediatric Pulmonology and
Allergology, Dept of Paediatrics and
Adolescent Medicine, Medical University
of Graz
Graz, Austria
ernst.eber@medunigraz.at

Ralf Eberhardt
Pneumology and Critical Care Medicine,
Thoraxklinik at the University
Heidelberg, and Translational Lung
Research Center Heidelberg, member of
the German Lung Research Foundation
Heidelberg, Germany
ralf.eberhardt@med.uni-heidelberg.de

Joseph Stuart Elborn
Faculty of Medicine, Health and Life
Sciences, Queen's University Belfast
Belfast, UK
s.elborn@qub.ac.uk

Diana Ernst
Dept of Rheumatology and
Immunology, Medizinische Hochschule
Hannover
Hannover, Germany
ernst.diana@mh-hannover.de

Matthew Evison
Manchester University NHS Foundation
Trust
Manchester, UK
m.evison@nhs.net

Santiago Ewig
Thoraxzentrum Ruhegebiet, Kliniken
für Pneumologie und Infektiologie, EVK
Herne und Augusta-Kranken-Anstalt
Bochum, Germany
ewig@augusta-bochum.de

Pierre-Emmanuel Falcoz
University Hospital
Strasbourg, France
pierre-emmanuel.falcoz@chru-strasbourg.fr

Leonardo M. Fabbri
Section of Cardiorespiratory and Internal
Medicine, Dept of Medical Sciences,
University of Ferrara, Ferrara, Italy
COPD Center, Institute of Medicine,
Sahlgrenska University Hospital,
University of Gothenburg, Gothenburg,
Sweden
leonardo.fabbri20@gmail.com

William Falconer
North Bristol NHS Trust
Bristol, UK
euanfalconer@doctors.org.uk

Alberto Fantin
Respiratory Disease and Lung
Function Unit, Dept of Medicine and
Surgery, University of Parma
Parma, Italy
af@albertofantin.com

Harald Farnik
Klinikum der Johann Wolfgang Goethe,
Universitat Frankfurt
Frankfurt am Main, Germany
Harald.Farnik@kgu.de

Ramon Farré
Unitat Biofísica i Bioenginyeria, Facultat
de Medicina i Ciències de la Salut
Barcelona, Spain
rfarre@ub.edu

Johanna Feary
Royal Brompton Hospital
London, UK
j.feary@imperial.ac.uk

Alessandro Ferrazza
Dept of Public Health and Infectious Diseases, University of Rome
'La Sapienza'
Rome, Italy
alessanro.ferrazza@uniroma1.it

Frits M.E. Franssen
CIRO, Center of Expertise for Chronic Organ Failure, Horn, and Dept of Respiratory Medicine, Maastricht University Medical Center
Maastricht, The Netherlands
fritsfranssen@ciro-horn.nl

Thomas Fuehner
Dept of Respiratory Medicine, Städtisches Klinikum Braunschweig gGmbH, Braunschweig, and Dept of Respiratory Medicine, Medizinische Hochschule Hannover
Hannover, Germany
fuehner.thomas@mh-hannover.de

Stefano Gasparini
Dept of Biomedical Sciences and Public Health, Università Politecnica delle Marche, Pulmonary Diseases Unit, Azienda 'Ospedali Riuniti'
Ancona, Italy
s.gasparini52@gmail.com

Jens Gottlieb
Dept of Respiratory Medicine, Medizinische Hochschule Hannover and Biomedical Research in End-Stage and Obstructive Lung Disease (BREATH), German Center for Lung Research (DZL)
Hannover, Germany
gottlieb.jens@mh-hannover.de

Andrea Gramegna
Dept of Pathophysiology and Transplantation, Università degli Studi di Milano, and Internal Medicine Dept, Respiratory Unit and Adult Cystic Fibrosis Center, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico
Milan, Italy
gramegna.med@gmail.com

Mark Greer
Dept of Respiratory Medicine, Medizinische Hochschule Hannover and Biomedical Research in End-Stage and Obstructive Lung Disease (BREATH), German Center for Lung Research (DZL)
Hannover, Germany
greer.mark@mh-hannover.de

Fabio Guarracino
AOUP, Critical care medicine
Pisa, Italy
fabioguarracino@gmail.com

Dorothee Gullentops
Respiratory Oncology Unit, Dept Respiratory Medicine, University Hospital KU Leuven
Leuven, Belgium
dorothee.gullentops@uzleuven.be

Josune Guzman
General and Experimental Pathology, Ruhr University
Bochum, Germany
Josune.Guzman@rub.de

Sylvia Hartl
Ludwig Boltzmann Institute of COPD and Respiratory Epidemiology
Vienna, Austria
hartl.sylvia@aon.at

Linnea Hedman
The OLIN-studies, Norrbotten County Council
Luleå, Sweden
linnea.hedman@norrbotten.se

Jeroen M. Hendriks
Thoracic and Vascular Surgery, Antwerp University Hospital,
Antwerp, Belgium
jeroen.hendriks@uza.be

Matthew Hind
Dept of Respiratory Medicine, Royal Brompton Hospital
London, UK
m.hind@rbht.nhs.uk

Clare Hooper
Worcestershire Acute Hospitals NHS Trust
Worcester, UK
clare.hooper1@nhs.net

Rudolf M. Huber
University of Munich, Pneumology
Munich, Germany
huber@med.uni-muenchen.de

J. Mike Hughes
National Heart and Lung Institute, Imperial College
London, UK
mike.hughes@imperial.ac.uk

Marc Humbert
Université Paris-Sud, Faculté de Médecine, Université Paris-Saclay; AP-HP, Service de Pneumologie, Hôpital Bicêtre, Le Kremlin-Bicêtre, France; and INSERM UMR_S 999, Hôpital Marie Lannelongue, Le Plessis Robinson, France
marc.humbert@aphp.fr

John R. Hurst
UCL Respiratory, University College London
London, UK
j.hurst@ucl.ac.uk

Anna Paola Iori
University 'Sapienza' of Rome, Hematology Division
Rome, Italy
E-mail: iori@bce.uniroma1.it

Wim Janssens
Dept of Chronic Diseases, Metabolism and Ageing, KU Leuven,
Leuven, Belgium
wim.janssens@uzleuven.be

Patrick Lauwers
Thoracic and Vascular Surgery, Antwerp University Hospital,
Antwerp, Belgium
patrick.lauwers@uza.be

Margareta Ieven
Laboratory of Medical Microbiology, University Hospital Antwerp, and Dept of Medical Microbiology, Vaccine and Infectious Disease Institute, University of Antwerp
Antwerp, Belgium
margareta.ieven@uantwerpen.be

Julius Janssen
Dept of Pulmonary Diseases, Canisius Wilhelmina Ziekenhuis
Nijmegen, The Netherlands
j.janssen@cwz.nl

Christian Karagiannidis
Dept of Pneumology and Critical Care Medicine, Cologne-Merheim Hospital, Kliniken der Stadt Köln gGmbH, Witten/Herdecke University Hospital
Cologne, Germany
Christian.Karagiannidis@uni-wh.de

Coenraad F.N. Koegelenberg
Division of Pulmonology, Dept of Medicine, Stellenbosch University and Tygerberg Academic Hospital
Cape Town, South Africa
coeniefn@sun.ac.za

Helen J. Lachmann
National Amyloidosis Centre, Division of Medicine, University College London Medical School, and Royal Free Hospital London NHS Foundation Trust
London, UK
h.lachmann@ucl.ac.uk

Daniel Langer
Dept of Rehabilitation Sciences, KU Leuven
Leuven, Belgium
Daniel.langer@kuleuven.be

Sylvie Lantuéjoul
Département de Pathologie, Pôle de Biologie et de Pathologie, Centre Hospitalier Universitaire A. Michallon, INSERM U 823-Institut A. Bonniot-Université J. Fourier
Grenoble, France
SLantuejoul@chu-grenoble.fr

Pierantonio Laveneziana
Sorbonne Université, INSERM, UMRS1158 Neurophysiologie respiratoire expérimentale et clinique, and AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service des Explorations Fonctionnelles de la Respiration, de l'Exercice et de la Dyspnée du Département 'R3S'
Paris, France
pierantonio.laveneziana@aphp.fr

Romain Lazor
Interstitial and Rare Lung Disease Unit, Lausanne University Hospital
Lausanne, Switzerland
Romain.Lazor@chuv.ch

Wei Shen Lim
Respiratory Medicine, Nottingham University Hospitals NHS Trust
Nottingham, UK
weishen.lim@nuh.nhs.uk

Robert Loddenkemper
Deutsche Gesellschaft für Pneumologie
Berlin, Germany
robert.loddenkemper@pneumologie.de

Marc C.I. Lipman
Respiratory Medicine, Royal Free London NHS Foundation Trust and University College London
London, UK
marclipman@nhs.net

Jane S. Lucas
University of Southampton and University Hospital Southampton NHS Trust
Southampton, UK
jlucas1@soton.ac.uk

John MacSharry
School of Medicine, University College Cork
Cork, Ireland
j.macsharry@ucc.ie

Sara Maio
Clinical Physiology Institute, CNR
Pisa, Italy
saramaio@ifc.cnr.it

Sara Mantovani
Dept of Thoracic Surgery, Sapienza University of Rome
Rome, Italy
saramantos88@hotmail.it

George A. Margaritopoulos
Interstitial Lung Disease Unit, Royal Brompton Hospital
London, UK
gmargaritop@yahoo.gr

Pier-Valerio Mari
Fondazione Policlinico Universitario A. Gemelli IRCCS
Rome, Italy
piervalerio.mari@gmail.com

Nick Maskell
Academic Respiratory Unit, University of Bristol, and Southmead Hospital
Bristol, UK
nick.maskell@bristol.ac.uk

Gilbert Massard
Dept of Medical Education, University of Luxembourg
Grand-Duchy of Luxembourg
gilbert.massard@uni.lu

Maria Gabriella Matera
Dept of Experimental Medicine, University of Campania Luigi Vanvitelli
Naples, Italy
mariagabriella.matera@unicampania.it

Veerle Matheeussen
Laboratory of Medical Microbiology, University Hospital Antwerp, and Dept of Medical Microbiology, Vaccine and Infectious Disease Institute, University of Antwerp
Antwerp, Belgium
veerle.matheeussen@uza.be

Claire McBrien
National Heart and Lung Institute
London, UK
c.n.mcbrien@gmail.com

Anne McLeer-Florin
Plateforme de Génétique Moléculaire des Cancers, Pôle de Biologie et de Pathologie, Centre Hospitalier Universitaire A. Michallon, INSERM U 823-Institut A. Bonniot-Université J. Fourier
Grenoble, France
AFlorin@chu-grenoble.fr

Andrew Menzies-Gow
Royal Brompton and Harefield NHS Foundation Trust
London, UK
a.menzies-gow@rbht.nhs.uk

Giovanni Battista Migliori
Servizio di Epidemiologia Clinica delle Malattie Respiratorie, Istituti Clinici Scientifici Maugeri IRCCS
Tradate, Italy
giovannibattista.migliori@fsm.it

Lénaïg Mescam-Mancini
Département de Pathologie et Plateforme de Génétique Moléculaire des Cancers, Pôle de Biologie et de Pathologie, Centre Hospitalier Universitaire A. Michallon, INSERM U 823-Institut A. Bonniot-Université J. Fourier
Grenoble, France
LMescam@chu-grenoble.fr

Cinzia Milito
Dept of Molecular Medicine, Sapienza University of Rome
Rome, Italy
cinzia.milito@uniroma1.it

Robert F. Miller
Infection and Population Health, University College London
London, UK
robert.miller@ucl.ac.uk

Marc Miravitlles
Pneumology Dept, Hospital Universitari Vall d'Hebron/Vall d'Hebron Research Institute (VHIR) Barcelona, Spain
mmiravitlles@vhebron.net

Luigi Moretti
Radiation Oncology, Institut Jules Bordet, Université Libre de Bruxelles
Brussels, Belgium
luigi.moretti@bordet.be

Alyn H. Morice
Hull York Medical School, University of Hull, Castle Hill Hospital
Cottingham, UK
a.h.morice@hull.ac.uk

Desmond M. Murphy
Dept of Respiratory Medicine, Cork University Hospital
Cork, Ireland
desmond.murphy@hse.ie

Mouhamad Nasser
Hospices Civils de Lyon, Dept of Respiratory Medicine, National Reference Center for Rare Pulmonary Diseases
Lyon, France
mouhamad.nasser@chu-lyon.fr

David Navajas
Unitat Biofísica i Bioenginyeria, Facultat de Medicina i Ciències de la Salut
Barcelona, Spain.
dnavajas@ub.edu

Yvonne Nussbaumer-Ochsner
Cantonal Hospital Schaffhausen, Division of Pneumology
Schaffhausen, Switzerland
yvonne.nussbaumer@spitaeler-sh.ch

Paul M. O'Byrne
Firestone Institute for Respiratory Health, St Joseph's Hospital, and Dept of Medicine, McMaster University
Hamilton, ON, Canada
obyrnep@mcmaster.ca

Mariaelena Occhipinti
Section of Respiratory Medicine, Dept of Experimental and Clinical Medicine, University of Florence
Florence, Italy
mariaelena.occhipinti@unifi.it

Dario Olivieri
Respiratory Disease and Lung Function Unit, Dept of Medicine and Surgery, University of Parma
Parma, Italy
dario.olivieri@unipr.it

Anne Olland
Hôpitaux Universitaires de Strasbourg
Strasbourg, France
anne.olland@chru-strasbourg.fr

Paolo Onorati
Sapienza University of Rome, Dept of Public Health and
Infectious Diseases
Rome, Italy
onoratip68@gmail.com

Paolo Palange
Dept of Public Health and Infectious Diseases, University of Rome
Rome, Italy
paolo.palange@uniroma1.it

Antonio Palla
Pulmonary Unit, University of Pisa
Pisa, Italy
antonio.palla@med.unipi.it

Martyn R. Partridge
National Heart and Lung Institute, Imperial College London
London, UK
m.partridge@imperial.ac.uk

Ricardo Pellegrino
Centro Medico Pneumologico Torino
Turin, Italy
info@pneumotorino.it

Claudio Piersimoni
United Hospitals, Regional Reference Mycobacteria Unit – Clinical Pathology Laboratory
Ancona, Italy
claudio.piersimoni@ospedaliriuniti.marche.it

Patrizia Pignatti
Allergy and Immunology Unit, Istituti Clinici Scientifici Maugeri, IRCCS Pavia
Pavia, Italy
patrizia.pignatti@icsmaugeri.it

Charlotta Pisinger
Center for Clinical Research and Prevention, Frederiksberg–Bispebjerg University Hospital, and Faculty of Health Science, University of Copenhagen
Copenhagen, Denmark
charlotta.pisinger@regionh.dk

Riccardo Pistelli
Complesso Integrato Columbus – Respiratory Medicine
Rome, Italy
riccardopistelli@h-columbus.it

Massimo Pistolesi
Section of Respiratory Medicine, Dept of Experimental and Clinical Medicine, University of Florence
Florence, Italy
massimo.pistolesi@unifi.it

Camilla Poggi
Dept of Thoracic Surgery, Sapienza University of Rome
Rome, Italy
camilla.poggi@uniroma1.it

Venerino Poletti
Diseases of the Thorax, G.B. Morgagni Hospital, Forli, Italy
Dept of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus, Denmark
venerino.poletti@gmail.com

Giovanni Poletti
Haematology Laboratory, Area Vasta Romagna
Pievestina, Italy
gpoletti1958@gmail.com

Michael I. Polkey
Dept of Respiratory Medicine, Royal Brompton and Harefield NHS Foundation Trust
London, UK
m.polkey@rbht.nhs.uk

Federica Pulvirenti
Dept of Molecular Medicine, Sapienza University of Rome
Rome, Italy
federica.pulvirenti.md@gmail.com

Isabella Quinti
Dept of Molecular Medicine, Sapienza University of Rome
Rome, Italy
isabella.quinti@uniroma1.it

Elisabeth Quoix
University of Strasbourg, University Hospital
Strasbourg, France
equoix@gmail.com

Klaus F. Rabe
Grosshansdorf Hospital, Centre for Pneumology and Thoracic Surgery, Grosshansdorf, Germany
k.f.rabe@kh-grosshansdorf.de

Anna Rask-Andersen
Uppsala University
Uppsala, Sweden
anna.rask-andersen@medsci.uu.se

Niels Reinmuth
Dept of Thoracic Oncology, Lung Clinic Gauting
Gauting, Germany
n.reinmuth@asklepios.com

Luca Richeldi
Fondazione Policlinico Universitario A. Gemelli IRCCS
Rome, Italy
luca.richeldi@policlinicogemelli

Paolo Rogliani
Dept of Experimental Medicine, University of Rome Tor Vergata
Rome, Italy
roglianp@uniroma2.it

Gernot Rohde
Medical Clinic I, Dept of Respiratory Medicine, J.W. Goethe University Hospital
Frankfurt am Main, Germany
gernot.rohde@kgu.de

Edoardo Rosato
Dept of Clinical Medicine, Clinical Immunology Unit-Scleroderma Center, Sapienza University of Rome
Rome Italy
edoardo.rosato@uniroma1.it

Sara Roversi
University of Modena Reggio Emilia, Medical and Surgical Sciences
Modena, Italy
rov_sara@yahoo.it

Nicola Santelmo
Hôpitaux Universitaires de Strasbourg
Strasbourg, France
nicola.santelmo@chru-strasbourg.fr

Bernd Schönhofer
Dept of Pneumology, Intensive Care and Sleep Medicine, Klinikum Siloah
Hannover, Germany
bernd.schoenhofer@t-online.de

Maren Schuhmann
Pneumology and Critical Care Medicine, Thoraxklinik at the University Heidelberg
Heidelberg, Germany
maren.schuhmann@med.uni-heidelberg.de

Macé M. Schuurmans
Cantonal Hospital Winterthur, Internal Medicine, Division of Pulmonology
Winterthur, Switzerland
mace.schuurmans@ksw.ch

Martina Sester
Dept of Transplant and Infection Immunology, Saarland University
Homburg, Germany
martina.sester@uks.eu

Pallav L. Shah
Royal Brompton Hospital and National Heart and Lung Institute, Imperial College London
London, UK
pallav.shah@imperial.ac.uk

Jane A. Shaw
Division of Pulmonology, Dept of Medicine, Stellenbosch University and Tygerberg Academic Hospital
Cape Town, South Africa
janeshaw@sun.ac.za

Arnaud Scherpereel
Pulmonary and Thoracic Oncology Department, Lille University Hospital (CHU)
Lille, France
arnaud.scherpereel@chru-lille.fr

Torben Sigsgaard
Aarhus University
Aarhus, Denmark
ts@ph.au.dk

Marzia Simoni
Clinical Physiology Institute, CNR
Pisa, Italy
marzia_simoni@libero.it

Anita K. Simonds
Sleep and Ventilation Unit, Royal Brompton and Harefield NHS Foundation Trust
London, UK
A.Simonds@rbht.nhs.uk

Markus Solèr
St Claraspital, Pneumologie
Basel, Switzerland
msoler@bluewin.ch

Giovanni Sotgiu
Clinical Epidemiology and Medical Statistics Unit, Dept of Medical, Surgical and Experimental Sciences, University of Sassari
Sassari, Italy
gsotgiu@uniss.it

Paolo Spagnolo
Section of Respiratory Diseases, Dept of Cardiac, Thoracic, Vascular Sciences and Public Health University of Padova
Padua, Italy
paolo.spagnolo@unipd.it

Antonio Spanevello
Division of Pulmonary Rehabilitation, Istituti Clinici Scientifici Maugeri, IRCCS Tradate, Italy and Dept of Medicine and Surgery, Respiratory Diseases, University of Insubria, Varese-Como, Italy
antonio.spanevello@icsmaugeri.it

Carolin Steinack
UniversitatsSpital Zurich, Division of Pulmonology
Zurich, Switzerland
Carolin.steinack@usz.ch

Antonino Di Stefano
Istituti Clinici Scientifici Maugeri, IRCCS, SpA Società Benefit, Divisione di Pneumologia e Laboratorio di Citoimmunopatologia dell'Apparato Cardio Respiratorio
Veruno, Italy
antonino.distefano@icsmaugeri.it

Robert A Stockley
University Hospital
Birmingham, UK
r.a.stockley@bham.ac.uk

Christian Taube
Dept of Pulmonary Medicine, University Hospital Essen – Ruhrlandklinik
Essen, Germany
christian.taube@rlk.uk-essen.de

Verena Tischler
Dr Senckenberg Institute of Pathology, University Hospital Frankfurt
Frankfurt, Germany
verena.tischler@kgu.de

Koliarne Tong
Dept of Respiratory and Sleep Medicine, John Hunter Hospital
Newcastle, Australia
koliarne.tong@hnehealth.nsw.gov.au

Thierry Troosters
Dept of Rehabilitation Science, KU Leuven
Leuven, Belgium
Thierry.troosters@kuleuven.be

Amanda Tufman
University of Munich - Campus Innenstadt, Division of Respiratory Medicine and Thoracic Oncology, member of the German Centre for Lung Research (DZL - CPC-M)
Munich, Germany
amanda.tufman@med.uni-muenchen.de

Panayota Tzani
Respiratory Disease and Lung Function Unit, Dept of Medicine and Surgery, University of Parma
Parma, Italy
ptzani@ausl.pr.it

Argyrios Tzouvelekis
Interstitial Lung Diseases Unit, Medical School, National and Kapodistrian University of Athens, Hospital for Diseases of the CHEST 'SOTIRIA'
Athens, Greece
argyrios.tzouvelekis@fleming.gr

Omar S. Usmani
National Heart and Lung Institute (NHLI), Imperial College London and Royal Brompton Hospital
London, UK
o.usmani@imperial.ac.uk

Francesco Vaccaro
Dept of Public Health and Infectious Disease, Sapienza University of Rome
Rome, Italy
francesco.vaccaro@uniroma1.it

Claudia Valenzuela
Hospital Universitario la Princesa
Madrid, Spain
claudiavale@hotmail.com

Paul Van Houtte
Radiation Oncology, Institut Jules Bordet, Université Libre de Bruxelles
Brussels, Belgium
paul.vanhoutte@bordet.be

Peter van Luijk
University of Groningen, University Medical Center Groningen
Groningen, The Netherlands
p.van.luijk@umcg.nl

Paul E. Van Schil
Thoracic and Vascular Surgery, Antwerp University Hospital,
Antwerp, Belgium
paul.van.schil@uza.be

Jacopo Vannucci
Dept of Thoracic Surgery, Sapienza University of Rome
Rome, Italy
jacopovannucci@tiscali.it

Federico Venuta
Dept of Thoracic Surgery, Sapienza University of Rome
Rome, Italy
federico.venuta@uniroma1.it

Geert M. Verleden
University Hospital Gasthuisberg, Dept Respiratory Disease, Lung Transplantation Unit
Leuven, Belgium
geert.verleden@uzleuven.be

Johny A. Verschakelen
University Hospitals Leuven
Leuven, Belgium
johny.verschakelen@uzleuven.be

Johan Vansteenkiste,
Respiratory Oncology Unit, Dept of Respiratory Medicine, University Hospital KU Leuven
Leuven, Belgium
johan.vansteenkiste@uzleuven.be

Giovanni Viegi
Clinical Physiology Institute, CNR, Pisa, Italy
Biomedical Research and Innovation Institute, CNR Palermo, Palermo, Italy
viegig@ifc.cnr.it

Dina Visca
Division of Pulmonary Rehabilitation, Istituti Clinici Scientifici Maugeri, IRCCS Tradate
Tradate, Italy
dina.visca@icsmaugeri.it

Duccio Volterrani
Nuclear Medicine Unit, University of Pisa
Pisa, Italy
duccio.volterrani@med.unipi.it

Florian von Groote-Bidlingmaier
Division of Pulmonology, Dept of Medicine, Stellenbosch University and Tygerberg Academic Hospital
Cape Town, South Africa
florianv@sun.ac.za

Woolf T. Walker
University of Southampton and University Hospital Southampton NHS Trust
Southampton, UK
Woolf.Walker@uhs.nhs.uk

Susan A. Ward
Human Bio-Energetics Research Centre
Crickhowell, UK
saward@dsl.pipex.com

Peter Wark
Centre for Healthy Lungs, Hunter Medical Research Institute, University of Newcastle, and
Dept of Respiratory and Sleep Medicine, John Hunter Hospital
Newcastle, Australia
Peter.wark@newcastle.edu.au

Athol U. Wells
Interstitial Lung Disease Unit, Royal Brompton Hospital
London, UK
RBHILD@rbht.nhs.uk

Tobias Welte
Dept of Respiratory Medicine, Medizinische Hochschule Hannover and Biomedical Research in End-Stage and Obstructive Lung Disease (BREATH), German Center for Lung Research (DZL)
Hannover, Germany
Welte.Tobias@mh-hannover.de

Jason Weatherald
Division of Respirology, Dept of Medicine, University of Calgary; and Libin Cardiovascular Institute of Alberta
Calgary, AB, Canada
jason.weatherald@ucalgary.ca

Mark Woodhead
University of Manchester
Manchester, UK
mark.woodhead@manchester.ac.uk

Jean-Pierre Zellweger
Swiss Lung Association –
TB Competence Center
Berne, Switzerland
zellwegerjp@swissonline.ch

Preface

> ‘The roots of education are bitter, but the fruit is sweet.’
> *Aristotle*

The *ERS Handbook of Respiratory Medicine*, first published in 2010, is a comprehensive and easily accessible source of state-of-the-art information on adult respiratory medicine.

In addition, it represents an invaluable resource for those preparing for the HERMES examination, those who require revalidation and those who wish to keep their knowledge up to date. As usual, the *Handbook* is organised into very concise, peer-reviewed chapters, written by leading experts in each specific field of respiratory medicine.

In this third edition, a complete revision of earlier versions is provided and, importantly, its content is closely aligned with the updated HERMES Respiratory Medicine syllabus. Although we tried to follow this principle as much as possible, for a complete and exhaustive *Handbook*, some extra chapters and topics are necessary to offer a comprehensive overview over all relevant topics in respiratory medicine.

This third edition of the Handbook includes new sections on:

- Inhaled and systemic pharmacotherapy
- Allergen-specific immunotherapy
- Lung transplantation
- Respiratory emergencies
- Upper airway disease
- Rare airway disease
- Congenital airway disease
- Aspiration pneumonitis
- Idiopathic pulmonary fibrosis
- Arteriovenous malformation
- Respiratory consequences of systemic/extrapulmonary conditions
- Primary ciliary dyskinesia
- α_1-antitrypsin deficiency
- Occupational diseases

We are grateful to the ERS Education Council, the ERS publications office and all contributors who made this third edition possible.

We hope that you will find this Handbook as useful a resource as the earlier editions and that you enjoy reading and using it!

Paolo Palange, Gernot Rohde
Chief editors

List of abbreviations

(C)HF	(Congestive) heart failure
AHI	Apnoea–hypopnoea index
AIDS	Acquired immunodeficiency syndrome
BMI	Body mass index
CF	Cystic fibrosis
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CT	Computed tomography
ECG	Electrocardiogram
ENT	Ear, nose and throat
$\mathrm{FEV_1}$	Forced expiratory volume in 1 s
FVC	Forced vital capacity
Hb	Haemoglobin
HIV	Human immunodeficiency virus
HRCT	High-resolution computed tomography
$K\mathrm{CO}$	Transfer coefficient of the lung for carbon monoxide
MRI	Magnetic resonance imaging
NIV	Noninvasive ventilation
OSA(S)	Obstructive sleep apnoea (syndrome)
$P\mathrm{aCO_2}$	Arterial carbon dioxide tension
$P\mathrm{aO_2}$	Arterial oxygen tension
PCR	Polymerase chain reaction
$P\mathrm{tcCO_2}$	Transcutaneous carbon dioxide tension
$S\mathrm{aO_2}$	Arterial oxygen saturation
$S\mathrm{pO_2}$	Oxygen saturation measured by pulse oximetry
TB	Tuberculosis
TLC	Total lung capacity
$T\mathrm{LCO}$	Transfer factor for the lung for carbon monoxide
$V'\mathrm{E}$	Minute ventilation

Anatomy of the respiratory system

Pallav L. Shah

Pleura

The lungs are covered by a fine membrane known as the pleura. The parietal pleura is the outer layer and the visceral pleura is adherent to the lungs. The two are in continuity with each other and there is a very fine space between the two, the pleural cavity. The parietal pleura is described according to the surface that it is adjacent to: costovertebral, diaphragmatic, cervical and mediastinal. There are also pleural recesses where the two different pleural surfaces are situated next to each other without any intervening lung in normal respiration. The costodiaphragmatic recesses are a thin area between the costal and diaphragmatic pleura. The costomediastinal recess is between the costal and mediastinal pleura, and is found behind the sternum and costal cartilages.

The pleura is supplied by its regional blood vessels. Hence, the cervical pleura is supplied by branches of the subclavian artery, the costovertebral pleura by the intercostal arteries and the diaphragmatic pleura from the vascular plexus from the surface of the diaphragm. The venous drainage occurs into the corresponding veins, which then drain into the vena cava. The lymphatic drainage is into the corresponding lymph nodes, *e.g.* the intercostal lymphatics drain into the posterior lymph nodes and then into the thoracic duct. The visceral pleura is supplied by the bronchial vessels and the lymphatics drain into the intercostal and peribronchial lymphatics. The parietal pleura is supplied by the regional nerves and contains the pain fibres. The costal and peripheral aspects of the diaphragmatic pleura are supplied by the corresponding intercostal nerves, whereas the diaphragmatic and mediastinal pleura are supplied by the phrenic nerves.

Key points

- The anatomy of the thorax can be divided broadly into the pleura, lungs, mediastinum, diaphragm and heart.
- The lungs can be further subdivided into lobes, segments, trachea and bronchi.
- The mediastinal space contains structures including the thymus gland, thoracic lymph nodes, thoracic duct, vagus nerve and autonomic nerve plexus.
- The thoracic structures include the vital organs for respiration and circulation. This chapter will focus on the pleura, lungs, mediastinum and diaphragm. The anatomy of the heart is not discussed.

Lungs

The apex of the lung extends into the thoracic inlet and on the anterior aspect lies above the first costal cartilage. On the posterior aspect, the apex of the lung is level with the neck of the first rib. At its highest position it is ~2.5 cm above the clavicle. The base of the lung is a concave structure and lies over the diaphragm. The main surface of the lung is the costal surface, which is smooth and shaped according to the chest wall. The medial surface of the lung is shaped posteriorly according to the vertebral column and medially by the heart. The lungs are also indented by the numerous vascular structures, such as the aorta, that are in contact with them.

The right lung consists of upper, middle and lower lobes (figure 1a). The left lung is composed of an upper and lower lobe (figure 1b). In the right lung there are two fissures. The oblique fissure separates the lower lobe from the upper and middle lobes. The smaller horizontal fissure separates the upper and middle lobes. In the left lung, the oblique fissure separates the upper lobe from the lower lobe.

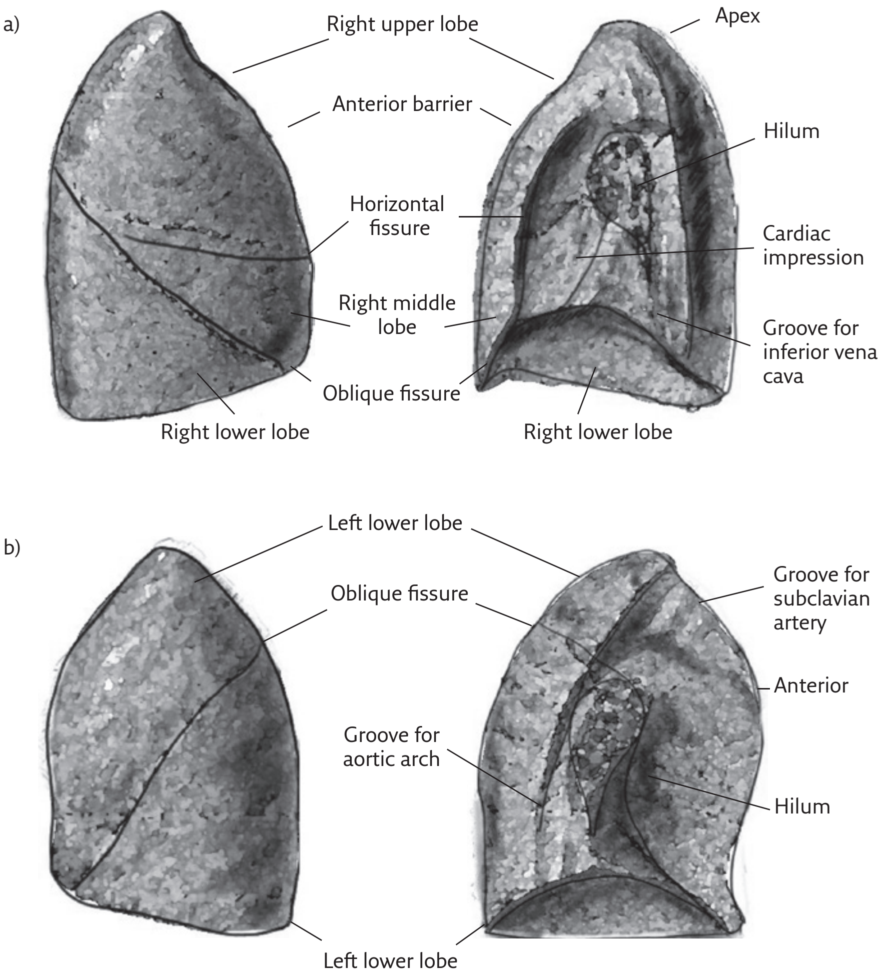

a)
Right upper lobe
Apex
Anterior barrier
Hilum
Horizontal fissure
Cardiac impression
Right middle lobe
Groove for inferior vena cava
Oblique fissure
Right lower lobe
Right lower lobe
b)
Left lower lobe
Groove for subclavian artery
Oblique fissure
Anterior
Groove for aortic arch
Hilum
Left lower lobe

Figure 1. Medial aspect of a) right and b) left lung. © P.L. Shah.

Bronchopulmonary segments

The main bronchi divide into lobar bronchi that, in turn, divide into segmental bronchi. Each divide into a structurally and functionally independent unit of tissue. The right lung consists of 10 bronchopulmonary segments: three in the upper lobe, two in the middle lobe and five in the lower lobe.

The left lung comprises nine segments: five in the upper lobe, including two within the lingula, and four in the lower lobes. There is no true medial segment in the left lower lobe as this area is occupied by the heart.

Each bronchus continues to subdivide into smaller, narrower airways until they finally form terminal bronchioles and then respiratory bronchioles, which are devoid of cartilage. These in turn lead to several alveolar ducts, which in turn end in several alveoli. The collective structure is termed an acinus. The secondary pulmonary lobule is the smallest part of the peripheral lung bounded by connective tissue, and usually consists of three to six pulmonary acini forming a hexagonal pattern with a central artery, lymphatic and peripheral veins.

Trachea and bronchi

The trachea (figure 2) is 100 mm long and ranges from 15 mm to 20 mm in diameter. It is made up of anterolateral cartilage rings with a fibromuscular posterior wall. The trachea divides at the level of the fourth vertebral body (level with the aortic arch) into the right and left bronchi. The right main bronchus is ~25 mm long (7–10 mm in diameter) and divides into the right upper lobe at the level of the fifth thoracic vertebra. It then continues as the bronchus intermedius, which is ~20 mm in length. The right main bronchus is wider, shorter and more vertical than the left main bronchus and, hence, foreign bodies tend to lodge more frequently into the right main bronchus. The bronchus intermedius then branches into the middle and lower lobes. The right middle lobe is formed on the anterior aspect of the bronchus intermedius. The right lower lobe bronchus gives off a branch to the superior segment and continues to descend posterolaterally, giving off branches to the medial, anterior, lateral and posterior segments of the lower lobe.

The left main bronchus is longer, measuring ~40 mm in length (7–10 mm in diameter), and enters the hilum of the left lung at approximately the level of the sixth thoracic vertebra. It divides into the left upper lobe and left lower lobe bronchus; the left upper lobe bronchus in turn gives off the superior division and supplies the apical posterior and anterior branches of the left upper lobe and the inferior division, which supplies the superior segment of the lingula and inferior segment of the lingula. The left lower lobe descends posterolaterally and first gives off a posteriorly located branch to the apical segment of the lower lobe and then gives branches to anteromedial, lateral and posterior basal bronchi.

The trachea is supplied superiorly by branches of the inferior thyroid arteries and more inferiorly by branches of the bronchial arteries. The venous drainage tends to be towards the inferior thyroid venous plexus and the lymphatic drainage to the pre-tracheal and para-tracheal lymph nodes. The bronchi and the airways are supplied by the bronchial arteries, which originate from the systemic circulation and arise either directly from the descending thoracic aorta or indirectly *via* the intercostal arteries. The venous drainage of the airways is more complicated and consists of deep bronchial veins that communicate with pulmonary veins which drain back into the left atrium. There are also superficial bronchial veins that drain into the azygos or the intercostal veins. The innervation of the endobronchial tree is *via* the anterior

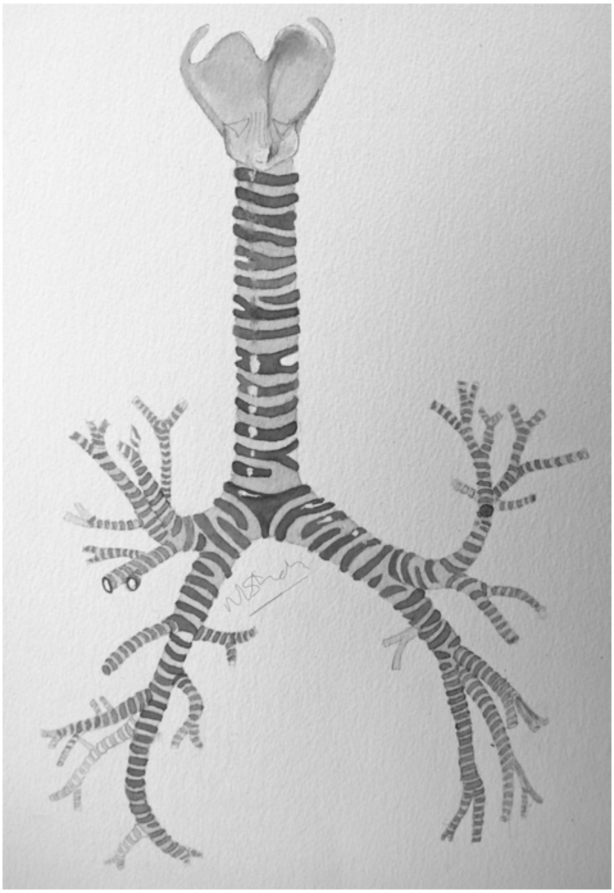


Figure 2. The trachea and bronchi. © P.L. Shah.

and posterior pulmonary plexus, which include branches from the vagus, recurrent laryngeal and sympathetic nerves.

Hila

The pulmonary hila join the medial aspect of the lung to the heart and the trachea. In each hilum, there are a number of structures either entering or leaving the structure. They include the main bronchi, pulmonary artery, superior pulmonary vein, inferior pulmonary vein, bronchial artery, bronchial vein, pulmonary autonomic neural plexus, lymphatics and loose connective tissue.

Pulmonary vasculature and lymphatic drainage

The pulmonary artery carries deoxygenated blood to the alveoli and the oxygenated blood then returns *via* the pulmonary veins to the left atrium. The pulmonary arteries lie anterior to the carina and the corresponding main bronchi. The artery then enters the lung *via* the hilum. On the right side, the upper lobe branch of the pulmonary arteries is anterior and lateral to the right upper lobe whereas the inferior branch of the pulmonary artery passes laterally and posterior to the lower lobe bronchus. On the left side, both upper and lower lobe pulmonary artery branches are lateral and posterior to the corresponding airways. The descending branch of the left pulmonary artery passes behind the left upper lobe and travels laterally and inferior to the left lower lobe bronchi.

There are two pulmonary veins on each side (superior and inferior pulmonary veins) that pass anterior and inferior to the pulmonary artery and bronchi. The lymphatic vessels drain into the hilar and subsequently into the tracheobronchial lymph nodes.

Mediastinum

The mediastinum is the space between the two lungs. The superior extent of the mediastinum is the thoracic inlet and the inferior extent is the diaphragm. The anterior border is the sternum and the posterior border is the vertebral column. It is divided into the superior, anterior, middle and posterior mediastinum. The mediastinum contains numerous structures, such as the thymus gland, thoracic lymph nodes, thoracic duct, vagus nerve and autonomic nerve plexus.

The thymus gland lies in the superior and anterior mediastinum. The lower border is down to the fourth costal cartilage. Its blood supply is derived from a branch of the internal thoracic artery and the inferior thyroid artery. The thymic veins drain into the left brachial cephalic vein and internal thoracic veins. The lymphatic drainage is into the tracheobronchial lymph nodes.

The mediastinum lymph nodes have special significance in the staging of lung cancer. They are found in the pre-tracheal, para-tracheal, subcarinal and para-oesophageal positions. They are classified according to the International Association for the Study of Lung Cancer (IASLC) lymph node map into lymph node stations (*e.g.* station 4 is the right paratracheal lymph node). The thoracic duct starts at the lower level of the 12th thoracic vertebra and enters the mediastinum through the aortic opening of the diaphragm. It runs in the posterior aspect of the mediastinum just right of the midline between the aorta and the azygos vein. In the superior mediastinum, it ascends onto the left side adjacent to the oesophagus. It finally terminates into one of the subclavian veins or the internal jugular vein.

The vagus nerve on the right side is found lateral to the trachea and posterior medial to the right brachiocephalic vein and super vena cava. It then passes behind the right main bronchus and continues to the posterior aspect of the right atrium. Here it divides into branches, which form the pulmonary autonomic plexus. The left vagus nerve is found between the left common carotid and subclavian artery and behind the left brachiocephalic vein. It crosses the aortic arch and passes behind the left hilum. Here, it divides and forms the pulmonary plexus. The autonomic nervous plexus in the mediastinum is formed from the vagus nerve, thoracic sympathetic chain and the autonomic plexus (cardiac, oesophageal and pulmonary plexus).

The right phrenic nerve descends laterally to the super vena cava anterior to the pulmonary hilar and then along the pericardium (over the right atrium) before reaching the diaphragm. The left phrenic nerve runs anteromedially to the vagus nerve above the aortic arch and then anteriorly to the left hilum. It then runs along the pericardium (covering the left ventricle) before supplying the diaphragm.

Diaphragm

The diaphragm is a musculofibrous sheet that separates the thorax and abdomen. It has an important role in the mechanism of breathing and coughing. It has a convex upper surface and is circumferentially attached to the lower aspect of the thorax by muscle fibres that converge to a central tendon. The diaphragm has three openings within it through which pass the inferior vena cava (at the level of eighth thoracic vertebra, T8), the oesophagus (T10) and the aorta (T12). Its blood supply is from the lower five intercostal arteries, the subcostal artery and the phrenic arteries. The venous drainage is from the phrenic veins, which drain into the inferior vena cava. The diaphragm is supplied by the phrenic nerve, which primarily originates from the C4, C5 and C6 cervical nerve root (the course of which is described above).

Development

The development of the respiratory system occurs at ~26 days of gestation with proliferation of a diverticulum that originates from the foregut. The laryngotracheal tube and main bronchi are formed first. Over the next 10 weeks, the lower conducting airways develop and, finally, the acinar structures develop. The alveoli and interstitial tissue are then formed. Alveolar development occurs from 28 weeks gestation and continues during early childhood.

Further reading

- Shah PL (2008). Pleura, lungs, trachea and bronchi. *In:* Standring S, ed. Gray's Anatomy. 40th Edn. London, Churchill Livingstone, pp. 989–1006.
- Shah PL (2008). Diaphragm and phrenic nerve. *In:* Standring S, ed. Gray's Anatomy. 40th Edn. London, Churchill Livingstone, pp. 1007–1012.
- Shah PL, *et al.* (2008). Mediastinum. *In:* Standring S, ed. Gray's Anatomy. 40th Edn. London, Churchill Livingstone, pp. 939–957.

Cytology of the lung

Venerino Poletti, Giovanni Poletti and Marco Chilosi

The role of cytological techniques for investigation of respiratory disorders has been recognised since the earliest days of clinical cytology. Improvement in sampling techniques and, in particular, the advent of fibreoptic bronchoscopy; transparietal fine-needle aspiration; cytological sampling assisted by echoendoscopy; the use of immunocytochemical and, more recently, molecular biology methods; recent advances in liquid-based cytology; and the use of cell block processing methods have increased the clinical impact of cytological diagnoses. Finally, the rapid, on-site analysis of cytological samples or of preparations obtained from bioptic samples (smears or touch imprints) has also improved the diagnostic yield of the investigative methods. A knowledge of 'basic cytology' should be part of the education for becoming a pulmonologist and this knowledge should be maintained in daily clinical practice.

Technical notes

The routine staining procedures that pulmonologists should be familiar with are Diff-Quik, May–Grünwald–Giemsa (MGG), Papanicolaou, haematoxylin–eosin, Gram staining, and staining for acid-fast bacilli (Ziehl–Neelsen and/or Kinyoun). Papanicolaou stain is a polychrome stain: the nucleus stains deep blue and nuclear details are sharp; the nucleolus stains red; the cytoplasm stains eosinophilic, cyanophilic or orange; and keratin stains deep orange. The slides must be wet-fixed swiftly and rapidly. Diff-Quik is a three-step procedure requiring about 20–30 s to complete. The staining kit includes fixative solution A (trimethane dye and methyl alcohol, but 95% ethyl alcohol is valid),

Key points

- Bronchoalveolar lavage (BAL) is an important source of cytological samples.
- Fine-needle aspiration has increased the impact of cytological diagnoses.
- Cell blocks are easy to prepare and useful for immunocytochemistry.
- Reactive cytological features in respiratory samples can be characteristic but nonspecific.
- Cytology can be used to diagnose respiratory infections.
- Lung carcinoma presents a variety of characteristic patterns.
- Lymphoproliferative disorders are more readily diagnosed in BAL fluid or fine-needle aspirates.
- Immunocytochemistry and molecular biology add to cytological diagnoses.

Table 1. Routine staining techniques

Stain	Advantages	Disadvantages
Papanicolaou	Very useful to detect and classify neoplastic cells identify viral inclusions	Time consuming
Diff-Quik	Very easy to perform for rapid, on-site examination	Not precise in defining nuclear details
MGG	The standard to classify 'haematologic' cells Very useful to identify viral cytoplasmic inclusions	Tends to overestimate 'dysplastic' changes
Gram	To identify and classify bacteria	
Kinyoun	For weakly acid-fast bacilli	

solution I that contains xanthene dye and solution II that contains a buffered solution of thiazine dyes. Slides are air dried and then fixed. Material obtained by fine-needle aspiration techniques should be used for smears and for cell-block preparations, cytofluorimetric analysis and genetic studies when deemed necessary. Summaries of the routine staining procedures, cytological preparations and genetic studies feasible on cytological material are presented in tables 1–3.

General cytological findings in respiratory samples

Squamous cells

Squamous cells are the most common cells in sputum but are less frequent in other specimens, being inconsistently found or absent. They appear as irregularly polygonal or rectangular cells with well-demarcated borders, small nuclei, and abundant clear pale cyanophilic to eosinophilic cytoplasm in Papanicolaou preps. The intermediate-type cells have a small central nucleus with thready chromatin and a lack of nucleoli.

Bronchial epithelial cells

Bronchial epithelial cells are columnar or triangular in shape and lie singly, in short ribbons or in flat sheets. They have a bluish grey cytoplasm with MGG or Diff-Quik stains, or are cyanophilic in Papanicolaou preparations, tapering at the point of previous anchorage.

Table 2. Routine 'cytological' preparations

Smear	Used for fine-needle aspiration samples rapid, on-site examination of bioptic material (squash or touch preparations)
Cytospin	The standard for cytological analysis of BAL fluid
Thin preparations	The standard for bronchial washing or lavage and pleural fluid
Cell block preparations	Easy to prepare Very useful for immunocytochemical studies
Flow cytometry	The standard for lymphocyte subset identification, and for demonstration of B-cell monoclonality and characterisation of myeloid cells

Table 3. The most frequently required investigations feasible on cytological material

EGFR mutations
ALK–EML4 fusion
BRAF^{V600E} mutation
MET expression
ROS1 rearrangement
PD-L1 expression
MicroRNA profiles
Heavy chain monoclonal rearrangement
T-cell receptor monoclonal rearrangement

Their nuclei vary considerably in size and shape but are usually basal, rounded or oval with open granular or condensed chromatin and a single small nucleolus.

Goblet cells

Goblet cells are columnar with a basally placed nucleus and supranuclear cytoplasm distended by globules of mucin. Cilia are absent. These cells increase in number in bronchial irritation.

Reserve cells

Reserve cells are small (slightly larger than lymphocytes), regular cells grouped to form sheets. Their nuclear/cytoplasmic ratio is high, the chromatin is coarse and there is a narrow rim of cytoplasm (green in Papanicolaou preps, or blue in Diff-Quik or MGG preps).

Club cells, Feyrter cells and type II pneumocytes

Club cells, Feyrter cells and type II pneumocytes are prone to rapid degenerative changes, and are not recognisable in respiratory samples unless hyperplastic/dysplastic.

Macrophages

Macrophages are round or oval cells, usually >10 µm in diameter, and possess generally abundant pale cytoplasm, with an oval or reniform nucleus showing a sharp nuclear membrane that is finely granular with evenly dispersed chromatin, micronucleoli and sometimes also macronucleoli. Binucleation is common and giant cells with numerous nuclei are not uncommon. These cells are phagocytic and their cytoplasm may be vacuolated or may contain small particles coated by iron, coarse granules of haemosiderin or inhaled particles.

Inflammatory cells

A variety of inflammatory cells may be recognisable in lung specimens:

- polymorphonuclear leukocytes
- lymphocytes
- eosinophils
- mast cells
- plasma cells

Megakaryocytes

Megakaryocytes can be identified in pulmonary arterial samples and may be misinterpreted as malignant.

Mesothelium

Tissue fragments of benign mesothelium are often collected during a transthoracic aspiration procedure. Most mesothelial tissue fragments appear as flat, two-dimensional sheets that present a honeycomb pattern. Mesothelial cells are, however, mainly found in pleural fluid. They are usually 15–30 μm in diameter but may be significantly larger. They may be present as solitary cells or in small cohesive clusters. The cytoplasm usually shows two zones: in Diff-Quik-stained smears, the endoplasm is lightly stained with peripheral, darker ectoplasm. The peripheral cell border is ruffled with blebs. As mesothelial cells imbibe water from the surrounding fluid, their cytoplasm may acquire a foamy macrophage phenotype. Mesothelial cell nuclei have crisp, thin nuclear membranes and evenly distributed, finely granular chromatin, one or two micronucleoli, and occasionally grooves.

Other components of respiratory samples

Mucus appears as a pale, thin, translucent shroud or as strings stained with varying intensity and with enmeshed cellular elements. Inspissated mucus appears as darkly stained blobs. Coils of compressed mucus are known as Curschmann's spirals and represent casts of the small bronchioles. Charcot–Leyden crystals, derived from the breakdown products of eosinophil granules, appear as orange-, yellow- or pinkish-stained diamond- or needle-shaped crystals. They are mainly observed in conditions evoking pulmonary eosinophilia. Calcific blue bodies and corpora amylacea are similar in routine preps. The former consists largely of calcium carbonate and shows central birefringence. Corpora amylacea are noncalcified, rounded structures composed of pulmonary surfactant proteins, epithelial membrane antigen and glycoproteins including amyloid. They stain pale pink, are Congo red positive and exhibit birefringence. Psammoma bodies (calcospherites) are laminated, nonrefractile, calcified concretions sometimes found in the presence of malignancy. Ferruginous bodies are formed when filamentous dust particles such as asbestos become coated with protein and iron in the lung parenchyma. They vary from 5 to 200 μm in length and are golden brown in colour with a characteristic segmented or beaded bamboo shape with knobbed or bulbous ends and stain blue with Perl's stain for iron. Other noncellular entities that may be found in respiratory specimens are calcium oxalate crystals (frequently associated with *Aspergillus* infection), Schaumann bodies, asteroid bodies, elastin fibres and amyloid.

Nonspecific reactive changes of the respiratory epithelium

Benign disorders of the respiratory tract may be manifested by characteristic but nonspecific abnormalities of the squamous epithelium, bronchial epithelium and alveolar epithelium. Reactive squamous cells from the upper respiratory tract have slightly enlarged, hyperchromatic nuclei. Anucleate, keratinised squamous cells, if present in large numbers, suggest an area of hyperkeratosis. Squamous metaplasia is defined as the replacement of the respiratory mucosa by squamous epithelium, and is a common reaction to injury in the trachea and bronchial tree. Particularly severe squamous atypia has been described in the trachea of patients with prolonged tracheal intubation and in tracheitis sicca occurring in patients who have permanent tracheostomy or in patients with tracheal inflammatory conditions, bronchial and parenchymal tuberculotic or mycotic lesions. Cells with squamous metaplasia may occur as single or small tissue fragments. The loss of cilia and the terminal plate (ciliocytophthoria) is a common response of the respiratory epithelium to acute injury; this phenomenon is observed mainly in viral infections. Papillary hyperplasia of the respiratory epithelium is most commonly observed in chronic inflammatory bronchial disorders (bronchiectasis and asthma), and appears cytologically as characteristic pseudopapillary cell clusters (Creola bodies) showing well-preserved bronchial epithelial cells with cilia, terminal plates or goblet cells at the periphery and a central core containing small cells. Reserve cell hyperplasia is represented by clusters of tightly packed small cells with uniform, dark, round or oval nuclei. Nucleoli may be observed but are tiny. Nuclear moulding is not present or at least not prominent. Type II alveolar cell hyperplasia has been typically reported bronchoalveolar lavage (BAL) fluid obtained from patients with acute respiratory distress syndrome but it is the cytological hallmark of diffuse alveolar damage (DAD) observed in a variety of acute lung disorders. Pneumocytes appear singly, in flat plates or in rosette-like groups, are polygonal or rectangular in shape, and have large nuclei with single or multiple prominent nucleoli and a pale or dense chromatin. The cytoplasm appears basophilic in Diff-Quik preps, often with vacuolation. Extracellular osmiophilic or metachromatic material representing fragments of hyaline membranes is sometimes surrounded by these reactive cells.

Cytological changes in pulmonary infections

Bacteria may be detected by specific stains, or by immunofluorescence or immunocytochemistry. Acid-fast mycobacteria are easily recognised when present in significant quantity in Ziehl–Neelsen preparations. *Nocardia*, a weakly acid-fast, aerobic, branching filamentous bacterium, is seen better using the Kinyoun method. *Actinomyces*, anaerobic or microaerophilic Gram-positive bacteria forming colonies of radiating, thin filamentous organisms, are better seen by silver staining. *Legionella* organisms are tiny Gram-negative bacilli that can be demonstrated by silver stains and by immunofluorescence. Numerous other cocci or bacilli may be recognised in Diff-Quik or MGG preps but are better identified using Gram staining. Granulomatous reaction, mainly associated with TB, is cytologically characterised by the presence, in fine-needle aspiration preparations, of pale histiocytes with elongated nuclei collected in nodular structures with poorly demarcated borders, surrounded by inflammatory cells (lymphocytes and neutrophils), necrosis and cellular debris. Malakoplakia due to *Rhodococcus equi* manifests cytologically with epithelioid macrophages with abundant foamy and granular cytoplasm, and intra- and extracytoplasmic, concentrically laminated bodies (Michaelis–Gutmann bodies).

Viral infections may determine cytopathic effects providing a background to the diagnosis. Furthermore, necrosis, inflammation, ciliocytophthoria, and bronchial and alveolar cell hyperplasia/dysplasia may be associated with these cytopathic changes or may be the only cytological manifestation of these infections. The cellular alterations suggesting a herpes simplex infection are: cells with multiple nuclei that may contain eosinophilic irregular inclusion bodies with a halo separating the inclusion from the nuclear membrane (Cowdry type A inclusions) (figure 1) or exhibit a peculiar type of nuclear degeneration that appear as slate grey, homogenised contents (Cowdry type B inclusions). Cells infected by cytomegalovirus are larger with large, amphiphilic, smooth, intranuclear inclusions surrounded by very prominent halos and marked margination of chromatin on the inner surface of the nuclear membrane. Intracytoplasmic small inclusions well seen by Diff-Quik or MGG stains are also identifiable. Infection with adenovirus produces two types of intranuclear inclusions: the first consists of a small red body surrounded by a well-circumscribed clear halo

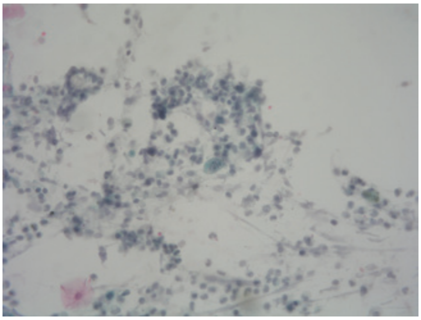


Figure 1. BAL sample showing a multinucleated cell with typical Cowdry A nuclear inclusions in herpes simplex pneumonitis in a transplanted patient. Papanicolaou staining.

and the second is a homogenous basophilic mass almost completely replacing the nucleus. The most characteristic cytological finding in measles pneumonia is the presence of multinucleated giant cells containing eosinophilic inclusions both within the nucleus and cytoplasm. Respiratory syncytial virus also stimulates a proliferation of multinucleated giant cells with cytoplasmic basophilic inclusions surrounded by halos. Other viruses that may give characteristic inclusions in respiratory cells are parainfluenza viruses, polyomavirus and human papillomavirus. Immunoreactivity using specific monoclonal antibodies increases the capacity to recognise virus elements in cytological specimens.

Fungal infections may also be documented cytologically; however, the distinction between colonisation and pneumonia requires clinical and radiological data. *Candida* species may appear as small, oval, 2–4-µm budding yeasts; occasionally, they may elongate into pseudohyphal forms with additional budding at the points of constriction. Filamentous fungal organisms are identified by routine stains but silver staining is more precise in identifying septation and the angle of branching. Fragmented hyphae usually identified in silver methenamine-stained preps along with numerous eosinophils, necrotic debris and neutrophils are the cytological hallmark of allergic bronchopulmonary aspergillosis. As angioinvasive mycoses are associated with parenchymal haemorrhage, iron-laden macrophages are usually found in the background. *Cryptococcus* may be identified also using a simple technique: adding some drops of India ink to the sample, the fungus appears as transparent oval or round microorganisms in a dark background. *Pneumocystis jirovecii* is easy to identify in BAL fluid using routine stains: finely vacuolated or foamy proteinaceous casts are typical. Diff-Quik or MGG preps are useful to recognise cysts and, within cysts, up to eight tiny, dot-like trophozoites or sporozoites, measuring 0.5–1 µm in diameter. The wall of the cyst is also stained by Grocott's methenamine silver stain. Numerous fungi are identifiable by routine staining procedures or using silver staining or immunocytochemistry using monoclonal antibodies.

Typical features may also be due to parasites (*Toxoplasma gondii*, *Entamoeba histolytica, Strongyloides stercoralis, Ancylostoma duodenale, Echinococcus, Paragonimus westermani,* microfilaria, *Dirofilaria* and *Microsporidium*).

Benign non-neoplastic disorders with characteristic cytological findings

Sarcoid granulomas have typical cytological features that are easy to recognise in fine-needle aspiration material and smears obtained by biopsy: nodular structures with sharp borders, consisting of epithelioid multinucleated cells in the central portion

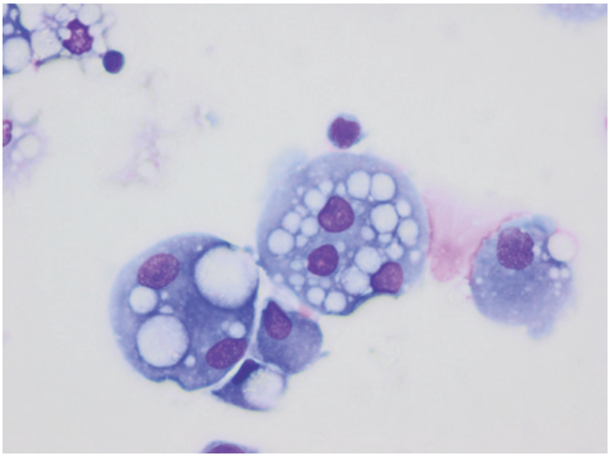


Figure 2. BAL sample showing macrophages containing large empty vacuoles. This feature is typically observed in lipid pneumonia. Diff-Quick preparation.

and of mature lymphocytes at the periphery. Alveolar proteinosis is the cause of a characteristic milky or opaque BAL fluid recovery; on microscopy, a dirty background consisting of amphiphilic granules is associated with the presence of globules or chunks of amorphous, amphiphilic, periodic acid–Schiff (PAS)-positive material. Foamy macrophages with PAS-positive cytoplasmic inclusions, cholesterol crystals, scattered hyperplastic type II pneumocytes and mature lymphocytes complete the pattern. Exogenous lipid pneumonia may be diagnosed when large macrophages with large cytoplasmic empty vacuoles (that may displace the nuclei at the periphery), or abundant bubbly or lacy, vacuolated cytoplasm are detected (figure 2). Oil material is easy to detect using Oil Red O or other specific stains. In BAL, an increase of lymphocytes may be an ancillary finding. In individuals smoking 'crack' cocaine, BAL fluid contains alveolar macrophages that accumulate large quantities of carbonaceous material in their cytoplasm; the material is also present extracellularly, imparting black discolouration to the specimen. Organising pneumonia, hypersensitivity pneumonitis, eosinophilic pneumonia, DAD, chronic or acute alveolar haemorrhage, amiodarone lung injury, pulmonary fat embolism, and rarer disorders (Gaucher's disease and Neimann–Pick disease) present characteristic or specific cytological features in BAL fluid. Organising pneumonia also presents characteristic aspects in touch imprints: globules of metachromatic purple amorphous material (Masson bodies) mingled with lymphocytes and scattered mast cells (figure 3). Cellular nonspecific pneumonitis, idiopathic or secondary and lymphocytic interstitial pneumonitis are usually associated with lymphocytosis in BAL fluid. Alveolar macrophages in smokers or recently former smokers show small brown or dark particles in the cytoplasm; these particles are Perl's positive because they also contain iron. In desquamative interstitial pneumonitis – which is, in most cases, a smoking-related interstitial disease – BAL eosinophilia along with smokers' macrophages is a typical finding. Giant cell pneumonitis, a hard-metal pneumoconiosis, is characterised by numerous giant cells with multiple nuclei and leukocytes in the cytoplasm (cannibalism); the metals may be documented by analytical electron microscopy. Cytotoxic effects of chemotherapy or radiation and chronic thermal injury determine alterations in nuclei and cytoplasm with aspects mimicking those observed in neoplastic cells (squamous metaplasia/dysplasia; multinucleation, nuclear enlargement with prominent nucleoli,

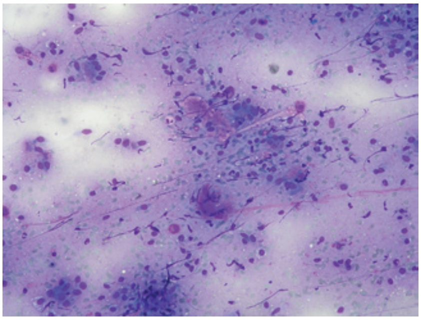


Figure 3. Touch imprint of a transbronchial lung biopsy showing balls of metachromatic, amorphous, extracellular material mingled with lymphocytes and scattered mast cells. Biopsy confirmed the diagnosis of organising pneumonia. Diff-Quick preparation, rapid on-site examination.

and nuclear or cytoplasmic vacuolisation). Immunocytochemistry is needed to identify Langerhans' cells (monoclonal antibodies against CD1a or langerin).

Lung tumours

Squamous carcinoma

The grading of squamous dysplasia is based on nuclear morphology, the amount of cytoplasm and the nuclear/cytoplasmic ratio. Well-differentiated keratinising squamous carcinomas are characterised by a polymorphous population of neoplastic cells: very large squamous cells may appear next to very small cells; spindly cells and tadpole cells are quite characteristic. In Papanicolaou preparations, the keratin accumulation in cytoplasm is easy to detect; the nuclei are hyperchromatic with coarsely textured chromatin, and irregular nucleoli are evident in poorly differentiated tumours. In nonkeratinising cancer, cytoplasm appears basophilic or amphiphilic. In fine-needle aspiration samples, neoplastic cells are more frequently grouped in sheets or smooth clusters. The background may be necrotic. Immunocytochemistry documents expression of p63/p40 protein in the nucleus. Thyroid transcription factor (TTF)-1 staining is negative.

Adenocarcinoma

Cell aggregates are a characteristic feature. These clusters have a three-dimensional papillary or approximately spherical configuration. Sheets or rosettes of neoplastic cells are frequent in fine-needle aspiration preparations. The papillary or acinar clusters of cancer cells may resemble and must be distinguished from Creola bodies. Cancer cells are large and usually round or polygonal, but occasionally columnar or cuboidal. Their nuclei are large, pleomorphic and eccentric, with a vesicular chromatin pattern and prominent nucleoli. The cytoplasm may contain mucin or appear vacuolated, mimicking that observed in foamy macrophages. The expression of TTF-1 is evident in nonmucinous adenocarcinoma cells. Immunocytochemistry (napsin positive and p63/p40 negative), and molecular biology investigations regarding *EGFR* mutations, MET expression, *ROS1* rearrangement, *ALK* rearrangement with the *EML4* gene and *BRAF*^{V600E} mutation are also feasible in cytological specimens.

Small cell lung cancer

In small cell lung cancer, the neoplastic cells are small and can be misidentified as lymphocytes in sputum. However, in samples obtained by fine-needle aspiration or in

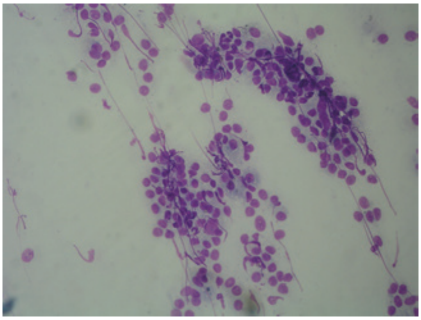


Figure 4. Touch imprint of a transbronchial biopsy showing cells two or three times larger than lymphocytes with nuclei showing a vesicular chromatin pattern, inconspicuous nucleoli and a small rim of cytoplasm. The neoplastic cells are in short chains and the moulding of adjacent nuclei in clusters of tumour cells is evident. The pattern is characteristic of small cell lung cancer.

smears from bioptic specimens, the proportion of well-preserved viable cells is larger, and they appear two or three times larger than lymphocytes, with nuclei showing a vesicular–granular chromatin pattern, inconspicuous nucleoli and a small rim of cytoplasm. The neoplastic cells are in short chains and the moulding of adjacent nuclei in clusters of tumour cells is very common (figure 4). Hyperchromatic or pyknotic cells and a necrotic background are other elements useful to confirm the diagnosis. Small cell carcinomas are predominantly TTF-1 positive, CD56 positive, chromogranin and/or synaptophysin positive, p63 negative, cytokeratin 5 negative and cytokeratin 8 positive. Tumour cells closely resembling small cell carcinoma may be observed in pulmonary cytology from children with lung metastases of neuroblastoma, embryonal rhabdomyosarcoma, Ewing's sarcoma, desmoplastic small round cell tumours, lymphomas and Wilms' tumours, and from adults with metastases of Merkel cell carcinoma, poorly differentiated synovial sarcoma and myxoid/round cell chondrosarcoma.

Large cell carcinoma

The cytological findings that suggest a diagnosis of large cell carcinoma are: disorganised groups of large pleomorphic cells or giant cells with clear malignant nuclear aspects (prominent nucleoli and coarse granulation of chromatin), intracytoplasmic neutrophils and a necrotic background. A neuroendocrine differentiation documented by immunocytochemistry (chromogranin, synaptophysin and CD56) is observed in a minority of cases.

PD-L1 assessment

PD-L1 testing is used to identify subjects that are most likely respond to immune checkpoint inhibitors, and may be performed in cytological cell blocks.

Carcinoid

Carcinoid tumours are usually cytologically diagnosed on fine-needle aspiration samples as they rarely, if ever, shed neoplastic cells into the sputum. Cells appear dispersed, isolated, in loosely cohesive groups or in syncytial tissue fragments, as cords, nests or anastomosing ribbons with an occasionally acinar pattern. They are small and round to cuboidal, with poorly defined cell borders and stippled chromatin. Some pleomorphic large cells with bizarre nuclei may also be detected. Spindle cells are more typical of the peripheral neoplasms. Markers such as chromogranin and synaptophysin are unequivocally positive; TTF-1 is negative. Necrosis and mitoses (or a significant positivity for Ki-67 (MIB-1)) suggest the diagnosis of atypical carcinoid.

Other malignant epithelial tumours

Other malignant epithelial tumours may be recognised by cytological criteria: adenoid cystic carcinoma (the diagnostic features are the presence of hyaline globules of basement membrane material with intervening small hyperchromatic cells), mucoepidermoid carcinoma and metastases (in these cases, immunocytochemistry may be diriment).

Lymphoproliferative and myeloid disorders

Primary lymphoid tumours in the lung are rare while lymph node-based lymphomas frequently affect the lung during the course of the disease. Acute myeloid leukaemia (M4–M5) may debut clinically with acute respiratory failure. These malignancies are more readily diagnosed on BAL or fine-needle aspiration preparations. Flow cytometry of suspended cells or immunocytochemistry, mainly on cell block preparations, are the usual ancillary studies required for a more precise definition of the lesions. Primary MALT (mucosa-associated lymphoid tissue) lymphomas in the lung are characterised by noncohesive lymphoid cells with centrocytic, monocytoid or plasmocytoid-like appearances (figure 5). Flow cytometry is necessary to identify a light chain monoclonal restriction. In addition, other low-grade B-cell lymphomas/leukaemias may be recognised by cytological and flow cytometry analysis. Specific chromosomal translocations involving the genes *MALT1* and *BCL10* may be detected, even in cytological specimens. Large B-cell lymphomas and highly malignant natural killer T-cell lymphomas may be captured by cytological/immunocytological analyses, and this may be sufficient to confirm lung recurrence but a cytological diagnosis in primary tumours is not feasible. Typical Reed–Sternberg (bilobed or multilobulated cells with distinct nucleoli and an abundant pale-grey cytoplasm on Diff-Quik or MGG preps) or Hodgkin cells (large mononuclear cells with prominent nucleolus and abundant cytoplasm), which are CD30 and CD15 positive, may be recognised in respiratory specimens associated with reactive, small, CD3-positive lymphocytes and scattered eosinophils, and this may confirm the diagnosis of relapse of the tumour in

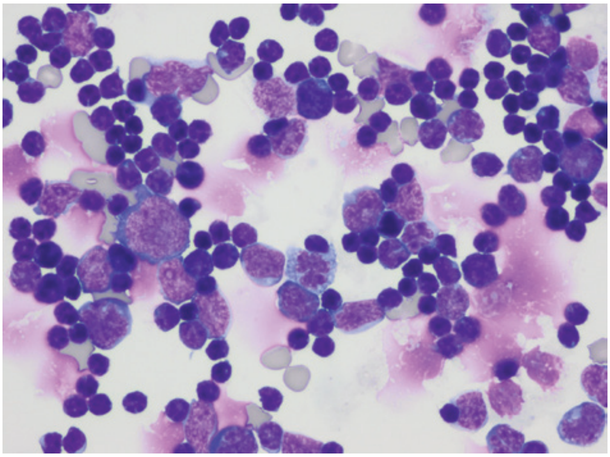


Figure 5. BAL sample showing atypical lymphocytes obtained from a patient with alveolar consolidation. The final diagnosis was B-cell lymphoma (MALT type). Diff-Quick preparation.

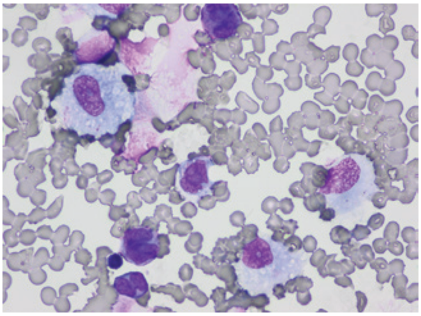


Figure 6. BAL sample showing myeloid blasts with almost cerebriform nuclei, evident nucleoli and sparse granules in the cytoplasm. Scattered alveolar foamy macrophages are also present. The sample is from a patient with acute promyelocytic leukaemia (M3), micrgranular variant. Diff-Quik staining.

the thorax. Myeloid neoplastic cells have been recognised in acute leukaemia, mainly M4 and M5, and in chronic myelomonocytic leukaemia, but also in other forms, either in BAL fluid or in fine-needle aspiration samples (figure 6).

Thymomas

Thymomas, although rare, are the most common thymic tumours in adults. Cytological findings are: cohesive aggregates of epithelial cells with an associated variable lymphocytic infiltration. Tissue fragments composed of epithelial cell aggregates intimately associated with lymphocytes are called lymphoepithelial complexes, and their presence is generally diagnostic of thymoma. There are two epithelial cell types in thymoma.

- Spindle/oval type, which possesses oval or fusiform, normochromatic nuclei with dispersed or unevenly distributed chromatin, indistinct or small nucleoli, and lightly stained or indistinct cytoplasm: type A or mixed (AB) thymoma
- Polygonal/round cells, which possess round, normochromatic, often clear nuclei, conspicuous round nuclei, and variable amounts of light green-stained cytoplasm: type B thymoma

Malignant thymic carcinomas present clear-cut cytological features of malignancy. Immunocytochemistry is useful to highlight epithelial cells or mature and immature lymphocytes.

Germ cell tumours

The mediastinum is the most common site for the development of extragonadal germ cell tumours. In seminoma, mixed inflammatory cells rich in lymphocytes surround cohesive malignant cells with delicate cytoplasm and a pale nucleus with prominent nucleoli. Embryonal carcinoma has a cytological aspect similar to adenocarcinoma. Yolk sac tumour (endodermal sinus tumour) is characterised by the presence of clusters of epithelial, highly malignant cells containing eosinophilic, PAS-positive, spherical hyaline bodies. Choriocarcinoma can be recognised in aspirates by the presence of large, multinucleated syncytiotrophoblastic cells with eosinophilic cytoplasm. Immunocytochemistry is very useful to mark the β-subunit of human chorionic gonadotropin or α-fetoprotein. Germ cell tumours may be a cause, along with Hodgkin's disease, of sarcoid-like granulomas collected by fine-needle aspiration techniques.

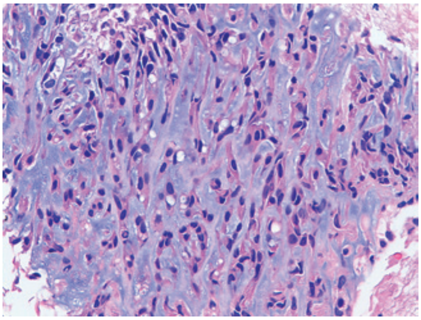


Figure 7. Cell block preparation obtained by echoendoscopic transoesophageal fine-needle aspiration. Spindle cells with eosinophilic cytoplasm are embedded in a myxoid stroma. Immunocytochemistry corroborated the diagnosis of gastrointestinal stromal tumour. Haematoxylin and eosin staining.

Mesenchymal tumours

Chondroid hamartochondromas may be easily recognised cytologically. In fine-needle aspiration samples, the combination of fibrillar myxoid connective tissue, hyaline cartilage, and entrapped bronchiolar epithelium and fat are pathognomonic. The cytological features that are more or less distinctive of other benign or malignant neoplasm of mesenchymal origin (primary in the lung or metastatic) have been described for sclerosing haemangioma (pneumocytoma), granular cell tumour, solitary fibrous tumour, meningioma, schwannoma, gastrointestinal stromal tumour (figure 7), neurofibroma, ganglioneuroma, glomus tumour, pulmonary blastoma, ganglioneuroblastoma, melanoma, glioblastoma and a wide variety of sarcomas. Cytology in malignant mesothelioma has been thoroughly investigated, as collection of pleural fluid is very easy during thoracentesis, and cytological features of malignancy and immunocytological markers (calretinin, *etc.*) indicating the origin of neoplastic cells are now well known.

Further reading

- Adams J, *et al.* (2012). The utility of fine-needle aspiration in the diagnosis of primary and metastatic tumors to the lung: a retrospective examination of 1,032 cases. *Acta Cytol*; 56: 590–595.
- Allen TC, *et al.* (2013). Mesenchymal and miscellaneous neoplasms. *In*: Hasleton P, *et al.*, eds. Spencer's Pathology of the Lung. Cambridge, Cambridge University Press; pp. 1224–1316.
- Borie R, *et al.* (2011). Clonality and phenotyping analysis of alveolar lymphocytes is suggestive of pulmonary MALT lymphoma. *Respir Med*; 105: 1231–1237.
- Chilosi M, *et al.* (2010). Mixed adenocarcinoma of the lung: place in new proposals in classification, mandatory for target therapy. *Arch Pathol Lab Med*; 134: 55–65.
- Giles TM, *et al.* (2010) Respiratory tract. *In*: Gray W, *et al.*, eds. Diagnostic Cytopathology. Philadelphia, Churchill Livingstone Elsevier; pp. 17–111.
- Kini SR (2002). Color Atlas of Pulmonary Cytopathology. New York, Springer.
- Koss L, *et al.*, eds. (2006). Koss' Diagnostic Cytology. Philadelphia, Lippincott Williams & Wilkins.
- Linssen KC, *et al.* (2004). Reactive type II pneumocytes in bronchoalveolar lavage fluid. *Acta Cytol*; 48: 497–504.

- Murer B, *et al.* (2013). Metastases involving the lungs. *In*: Hasleton P, *et al.*, eds. Spencer's Pathology of the Lung. Cambridge, Cambridge University Press, pp. 1375–1407.
- Parham DM, *et al.* (1993). Cytologic diagnosis of respiratory syncytial virus infection in bronchoalveolar lavage specimen from a bone marrow transplant recipient. *Am J Clin Pathol*; 99: 588–592.
- Poletti V, *et al.* (2007). Bronchoalveolar lavage in malignancy. *Semin Respir Crit Care Med*; 28: 534–545.
- Poletti V, *et al.* (2015). Lymphoproliferative lung disorders. *In*: Cottin V, *et al.*, eds. Orphan Lung Diseases. London, Springer Verlag; pp. 493–515.
- Ravaglia C, *et al.* (2012). Diagnostic role of rapid on-site cytologic examination (ROSE) of broncho-alveolar lavage in ALI/ARDS. *Pathologica*; 104: 65–69.
- Solomides CC, *et al.* (2015). Respiratory tract. *In*: Bibbo M, *et al.*, eds. Comprehensive Cytopathology. 4th Edn. London, Elsevier Inc., pp. 427–287.
- Shidham VB, *et al.* (2010). Serous effusions. *In*: Gray W, *et al.*, eds. Diagnostic Cytopathology. Philadelphia, Churchill Livingstone Elsevier, pp. 115–175.
- Tabatowski K, *et al.* (1988). Giant cell interstitial pneumonia in a hard metal worker. Cytologic, histologic and analytic electron microscopic investigation. *Acta Cytol*; 32: 240–246.
- Travis WD, *et al.* (2015). A WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, IARC Press.
- Vlajnic T, *et al.* (2018). Detection of ROS-1 positive non-small cell lung cancer on cytological specimens using immunocytochemistry. *Cancer Cytopathol*; 126: 421–429.

Immunology and defence mechanisms

Antonino Di Stefano and Bruno Balbi

COPD is associated with chronic inflammation of the airways and lung parenchyma, which further increases during exacerbations of the disease. The aetiology of COPD is due to numerous complex interactions between environmental and genetic factors. Cigarette smoking exposure is the cause of >90% of COPD in industrialised countries. In developing countries, other factors such as burning biomass fuels for cooking and heating may be important causes of COPD. The interaction of the inflammatory process with oxidative stress and bacterial/viral infections plays a fundamental role in the progression of airflow limitation and disease manifestations. Small airways remodelling and pulmonary emphysema are likely to be the results of chronic inflammation interacting with external challenges. While the pattern of cellular prevalence in the small airways and parenchyma of COPD patients is well-established, more research is needed to clarify the different patterns of lung inflammation and immune response in relation to the different phenotypes of COPD and how inflammation changes over time and in response to therapy in these different phenotypes. Pathology studies show that chronic inflammation in the COPD lung increases as the disease progresses. However, the functional role of these inflammatory cells, T-cell subsets and structural cells is under constant investigation in stable and exacerbated COPD, and in patients at different stages of the disease. Relevant inflammatory pathways related to these inflammatory and structural cells are also the object of ongoing investigation to better define the potential molecular mechanisms involved in the COPD progression. In this section, we discuss the role of inflammatory cells, as well as the innate and adaptive immune response and bacterial/viral challenges in the pathogenesis of COPD.

Inflammatory cells

Airways and lung inflammation in stable COPD are characterised by an increased number of neutrophils, macrophages, T-lymphocytes and dendritic cells. The increased number

Key points

- Specific innate and adaptive host immune responses develop in the lung of patients with COPD. These inflammatory changes play a key role in the respiratory system altering the host defence mechanisms of these patients.
- T-lymphocytes, B-lymphocytes, macrophages, dendritic cells, neutrophils, ILCs and NK cells are involved in orchestrating the immune response in diseased lungs.
- Changes in the immune response and cellular activation play a role in determining different phenotypes of COPD.

of neutrophils is particularly evident in severe disease. The interaction of lymphocytes and macrophages may orchestrate the progression and severity of airway inflammation. The functional role of $CD3^+$ cells and their subsets $CD4^+$ and $CD8^+$ in the pathogenesis of COPD is an area of ongoing research. T-lymphocytes, mainly $CD8^+$ cells, are predominant in the bronchial biopsies of stable COPD patients. However, smokers with normal lung function also show, to a lesser extent, an increased number of $CD8^+$ cells in their bronchial mucosa, suggesting that the T-lymphocyte increase may be an effect of the smoking habit. Recently, Hogg *et al.* (2004) reported that the number of $CD4^+$ and $CD8^+$ cells in the small airways is higher in smokers with COPD compared to control smokers with normal lung function, and increases as the severity of COPD progresses. Mature $CD4^+$ and $CD8^+$ T-cells co-expressing the nuclear factor-kB p65 subunit (and thus with a greater capability to cause tissue damage) were found to be more numerous in bronchial biopsies of COPD patients than control subjects. A T-helper (Th)1/Tc1 immune response develops in stable mild/moderate COPD patients as confirmed by the finding of an enhanced expression of the transcription factor signal transducer and activators of transcription (STAT)4 in bronchial biopsies of these patients compared to control smokers and nonsmokers. Interferon (IFN)-γ immune expression is positively correlated with hosphor-STAT4 immune expression and its level is higher in COPD patients than control subjects, supporting the notion of a prevalent Th1/Tc1 immunological response in mild/moderate disease. Interestingly, there was a significant increase in markers of the innate immune response, such as interleukin (IL)-7 and IL-27 (involved in increased T-cell survival and Th1/Tc1 maturation, respectively) in bronchial biopsies of COPD patients compared to control nonsmokers. Their numbers correlated positively in the bronchial submucosa of all COPD patients, suggesting a significant role for these cytokines in the immune regulation of the inflammatory response in COPD. Recently, an anti-inflammatory and immunoregulatory role for IL-27 has been proposed since this cytokine up-regulates IL-10 expression and may develop Th17 inhibitory functions in rheumatoid arthritis and other autoimmune diseases. In contrast, IL-18, caspase-1 and IL-1β, related to inflammasome activation, were poorly expressed and unchanged in the bronchial biopsies of stable COPD patients compared to control groups. The inflammasome inhibitory molecules NALP7 (NACHT, LRR and PYD domains-containing protein 7) and IL-37 were increased in patients with COPD compared to control smokers, again supporting a minor role for inflammasome activation in stable COPD (figure 1).

Th17 cells, producing IL-17A and IL-17F, regulate neutrophilic and macrophage inflammation. γδ T-cells, natural killer (NK) cells and structural cells also express IL-17. The expression of IL-17A by neutrophils and macrophages has also been reported. IL-17A level is increased in the sputum of stable COPD patients compared to control subjects. $IL\text{-}17A^+$ and $IL\text{-}22^+$ cells are increased in the bronchial mucosa of COPD patients compared to control nonsmokers, and these two cytokines are mainly expressed in endothelial cells ($CD31^+$ cells). Increased levels of IL-17A and CXCL12 in the lymphoid follicles of severe COPD patients may play a role in the increased peripheral lung inflammation in severe disease. These data show a significant role for Th17 related cytokines in the pathogenesis and progression of COPD (figure 2).

Innate and adaptive immune response

Lymphoid follicles are present in the small airways of COPD patients more than in control subjects, and they are mainly composed of memory B-lymphocyte aggregates. The B cell-activating factor (BAFF) is increased within follicles and B-lymphocytes are oligoclonal (specific IgG production is increased) suggesting that these anatomical structures play a role in local antigen-specific immune responses in the peripheral lung.

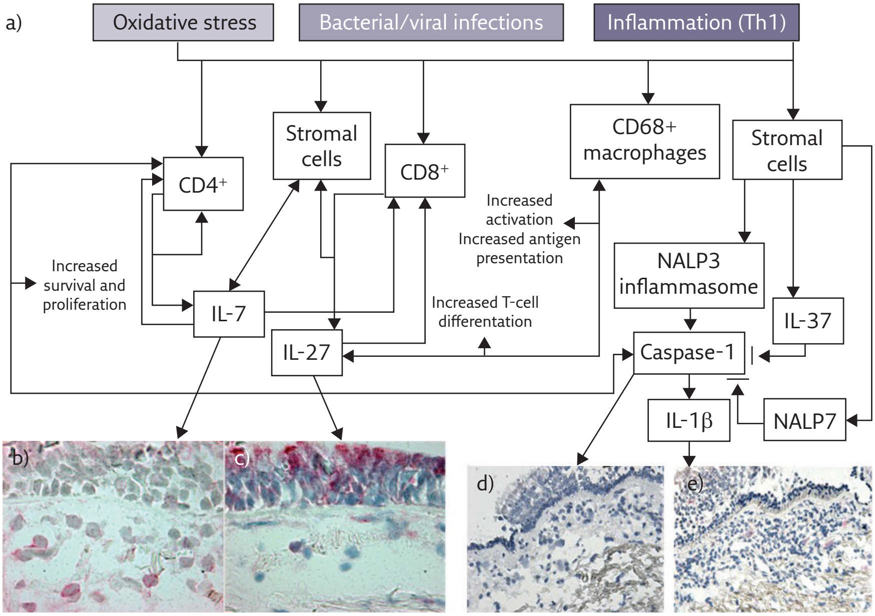

a)
Oxidative stress
Bacterial/viral infections
Inflammation (Th1)
Stromal cells
CD8+
CD68+ macrophages
Stromal cells
CD4+
Increased activation
Increased antigen presentation
Increased survival and proliferation
NALP3 inflammasome
IL-7
Increased T-cell differentation
IL-37
IL-27
Caspase-1
IL-1β
NALP7
b)
c)
d)
e)

Figure 1. a) Schematic representation of the innate immune response and inflammasome in the bronchial mucosa of patients with COPD. b–e) Immunohistochemistry performed in bronchial biopsies from a representative COPD patient: b) IL-7, c) IL-27, d) caspase-1 and e) IL-1β. NALP: NACHT, LRR and PYD domains-containing protein.

There are two resident types of B-cells in the lung: plasma cells, which are able to produce polymeric immunoglobulins (mainly IgA and IgM) and are secreted into the airway lumen; and memory B-cells generated during pulmonary infections, which are capable of inducing a secondary immune response to infections. Activated B-cells contribute to lymphoid follicle formation in the lung. The high affinity binding of antigen to B-cells induces B-cell proliferation and maturation into plasma cells expressing immunoglobulins. A T-cell dependent B-cell activation, causing the release of specific cytokines, is required and it develops in the chronically inflamed lungs of COPD. A T-cell independent B-cell activation may occur when microbial products bind their specific B-cell receptors. This B-cell activation induces a rapid immunoglobulin production by plasma cells. Lymphoid follicles are rarely present in the small airways of nonsmokers; they are present to a modest degree in the small airways of smokers with normal lung function, whereas they are particularly increased in the small airways of severe–very severe COPD patients.

Oligoclonal B-cells have been identified in lymphoid follicle patients with COPD, suggesting a role for these cells in the immune response to microbial antigens or antigens derived from extracellular matrix (ECM) breakdown products or smoking challenge. B-cells are activated by BAFF. BAFF is increased within follicles in severe–very severe COPD and in emphysema. Increased B-cell counts have also been reported in the large airways (bronchial biopsies) of COPD patients. Recently, it was observed that the majority of follicular B-cells were IgM$^+$ (70–80%) and that there were double the number of IgA$^+$ B-cells in lymphoid follicles of severe COPD compared to controls. Also, in severe COPD, an increased number of T-cells producing interleukin (IL)-21, activating immunoglobulin production, was present. Antibodies produced by plasma cells may also activate complement components, generating complement products that activate leukocytes. Increased sputum levels of complement-5 activation products have been reported in

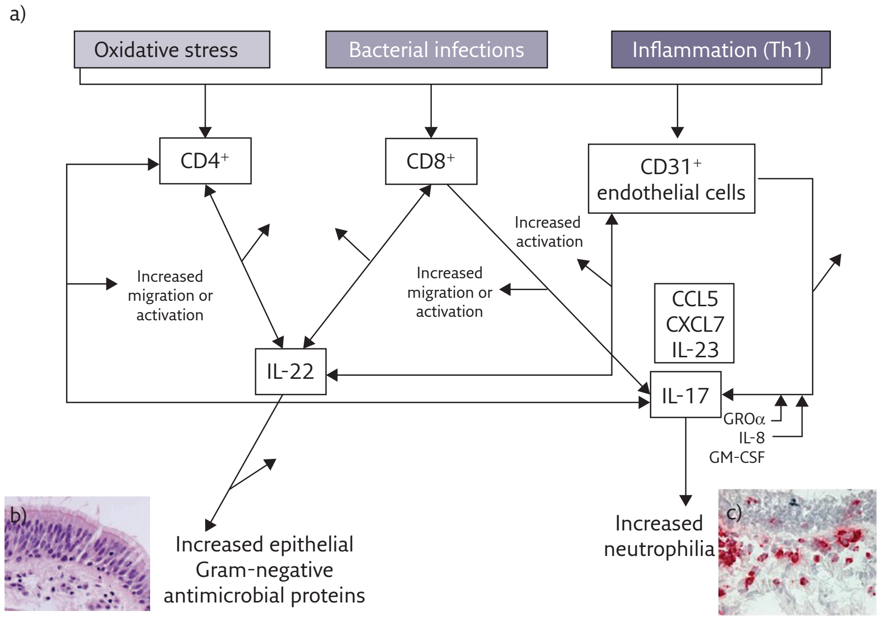

a)
Oxidative stress
Bacterial infections
Inflammation (Th1)
CD4+
CD8+
CD31+ endothelial cells
Increased activation
Increased migration or activation
Increased migration or activation
CCL5
CXCL7
IL-23
IL-22
IL-17
GROα
IL-8
GM-CSF
Increased epithelial Gram-negative antimicrobial proteins
Increased neutrophilia
b)
c)

Figure 2. a) Schematic representation of the Th17-related cytokines in the bronchial mucosa of patients with COPD. b, c) Histochemistry and immunohistochemistry performed in bronchial biopsies from a representative COPD patient: b) Haematoxylin–eosin and c) neutrophil elastase. GROα: growth-regulated oncogene-α; GM-CSF: granulocyte–macrophage colony-stimulating factor.

COPD, and they correlated negatively with lung diffusion coefficient in these patients, suggesting that leukocyte recruitment and proteinases release caused by complement-5 activation may play a role in air space enlargement in COPD patients.

NK and type-1 innate lymphoid cells (ILC1) have been recently identified as distinct cell populations based on their cytokine and transcription factors expression. Interestingly, recent works show that transforming growth factor (TGF)-β favours the conversion of NK cells into intermediate ILC1 cells and this phenotypic switch is functionally significant as the increased presence of ILC1 cells was unable to control tumour burden or viral load in a mouse model. As a consequence, alterations in the ILC1/NK ratio may be important in evaluating the local cytotoxic immune efficiency in different diseases including COPD and lung tumours. Our data on a reduction of TGF-β in the peripheral lung of COPD patients compared to control subjects may also represent an increased risk for lung tumour development in COPD patients. The number of NK cells counted in bronchial biopsies was relatively low, even though it was significantly higher in severe–very severe COPD patients compared to control smoking subjects. Granzyme B expression and cytotoxicity of NK cells were increased and the inhibitory NK receptor CD94 (Kp43) was decreased in the bronchoalveolar lavage (BAL) from patients with COPD compared to control subjects. Consequently, the toxicity of lung NK cells was higher in COPD patients than control subjects, contributing to the emphysema progression in these patients. Innate lymphoid cells are considered early orchestrators of the immune response and respond to a variety of stimuli by expressing an array of cytokines involved in subsequent immune responses. Group 1 ILC are mainly expressed in COPD where they contribute to IFN-γ-mediated inflammation. Group 2 ILC produce IL-5 and IL-13, contributing to type 2-mediated inflammation. Group 3 ILC are able to produce abundant IL-22 and seem to be more relevant in intestinal inflammation and psoriasis. These authors observed a trend to a higher frequency of the LC3 group in the lungs of patients with COPD compared to control subjects. Further studies are needed to better define which subgroups of ILCs are prevalent in COPD patients of increasing severity and their specific role in orchestrating the immune response in these patients.

Macrophages may play an important role in orchestrating the inflammatory process in COPD through the release of pro-inflammatory mediators including proteases, cytokines, chemokines and oxidative-stress related molecules. These cells in patients with COPD showed reduced phagocytic activity, which may increase the persistence of the inflammatory process and impair the clearance of bacterial viral pathogens. $CD68^+$ cells (macrophages) are increased in the bronchial mucosa of mild/moderate and severe/very severe COPD patients compared to control subjects. More recently, studies on phenotyping of macrophages in COPD have identified four distinct phenotypes of macrophages: a non-polarised macrophage (M0); an M1-type ($iNOS^+$, producing tumour necrosis factor-α, IL-1 and IL-12) more prone to inducing inflammation; an M2-type ($arginase^+$, producing TGF-β and IL-10) more prone to developing anti-inflammatory actions; and a dual positive M1–M2-type macrophage, showing a mixed picture of M1–M2 related cytokine production. The lung microenvironment in which these different types of macrophages are present is essential for macrophage polarisation and related function. One study showed that the number and percentage of $CD163^+$, $CD204^+$ and $CD206^+$ alveolar macrophages belonging to M2-type macrophages secreting more MMP9 were increased in severe/very severe COPD compared to mild disease and control subjects.

Phagocytosis of alveolar macrophages is impaired when these cells are exposed to air pollutants. Compared to control subjects, alveolar macrophages of COPD patients show impaired phagocytosis of *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*. Efferocytosis, the clearance of apoptotic neutrophils and structural cells, is an important process aimed at preventing the release of intracellular molecules causing secondary inflammation. This function is impaired in alveolar macrophages from COPD patients, particularly after smoking exposure. Impaired kinase signalling and a decreased ROS intracellular production have also been reported as molecular mechanisms contributing to the decreased phagocytosis/efferocytosis efficiency of alveolar macrophages in patients with COPD.

Dendritic cells are potent antigen-presenting cells with a key role in the regulation of immune responses. They also play a role in activating the memory T-cell responses. Dendritic cells are mainly divided into two types, myeloid and plasmacytoid, which partially differ in terms of their function and anatomic location. Mature $CD83^+$ dendritic cells are decreased in sputum of stable COPD patients compared to control groups. In the bronchial epithelium and submucosa, a reduction of dendritic cells has also been reported in COPD patients compared to control subjects. The chemokine receptor CCR5, which is involved in the uptake of microbial antigens and is expressed on myeloid dendritic cells, is reduced in patients with COPD. These data support the view of an impaired dendritic cell function in patients with COPD. More recently, however, increased NK cytotoxicity against lung epithelial cells, primarily mediated by lung dendritic cell priming *via* IL-15 and IL-15Rα, has been reported. Furthermore, at multi-colour flow cytometry, circulating plasmacytoid dendritic cells show an enhanced activation profile in patients with COPD, contributing to an increase of IFN-γ and IL-17-producing CD8+ T-cells. There is a need for more research to better define the precise role and functions of dendritic cell populations in orchestrating the T-cell-mediated immune response in patients with COPD.

There is an increased number of neutrophils present in the sputum, BAL, bronchial biopsies and peripheral airways of COPD patients compared to control subjects. Concomitantly, molecules stimulating the neutrophil migration and activation are also increased. Macrophage inflammatory protein-1α in the bronchial epithelium of severe COPD patients is increased with respect to mild COPD and control smokers. The analysis of pro-neutrophilic chemokines showed higher levels of RANTES (CCL5) and neutrophil activating protein-2 (CXCL7) in bronchial biopsies of severe stable COPD patients compared to control nonsmokers. Also present was an increased neutrophilic expression of CD44, involved in the increased neutrophilic adhesiveness to the ECM, or an increased neutrophilic expression of the activating receptor CD11b, particularly in the neutrophils from severe COPD compared to control subjects. These characteristics may contribute to an increased presence of these cells in the bronchial tissue of severe patients. The recently described release of neutrophil extracellular traps (NETs) is an important immune mechanism capable of capturing pathogens. An excess of NET formation damages the epithelium and may lead to lung tissue damage; it has also been reported in patients with COPD. Evasion of NETs by pathogens may increase resistance to the microbicidal components of NETs increasing the risk of airway infections in patients with COPD. More detailed studies are needed to better define the role of NET formation and its evasion in different clinical conditions of patients with COPD.

During exacerbations of COPD, an increased number of eosinophils has been reported in bronchial biopsies and sputum, together with increased neutrophils, T-lymphocytes, very late antigen-1 (involved in the T-cell recruitment) and tumour necrosis factor-α, in comparison to stable diseased patients. In severe COPD, with a further increase of neutrophilia, an upregulation of neutrophil-related chemokines such as ENA-78 (CXCL-5) and IL-8 (CXCL-8) has been reported. Eosinophilia, however, is transitory and these cells are poorly or non-degranulated and frequently confined to capillary vessels. These data support the anti-inflammatory treatments adopted in patients with COPD during exacerbations of the disease. The inflammatory response in different phenotypes of COPD patients, however, needs to be characterised more precisely.

Bacterial/viral challenges

In stable COPD, viruses and bacteria may cause acute exacerbations of the disease or they may amplify airway and lung chronic inflammation. Moreover, different bacterial species composing the lung microbiome contribute to the disease state in COPD and other lung diseases. In severe COPD, a reduction in microbial diversity with a relative increase of Proteobacteria and Actinobacteria and a reduction of Firmicutes phyla has been reported. The same authors also reported a significant association of $CD4^+$ cells with the extent of emphysema and bronchial infiltration. Exacerbations of COPD are associated with changes in airway microbiota and airway inflammation. The isolation of new strains of pathogens is associated with an increased risk of exacerbations. However, in published studies to date, there is no grading of the severity of exacerbations. Research designed to classify the exacerbation process related to COPD severity is needed in order to better define the role of the microbiome in the disease state in COPD. COPD patients have a greater total viral load than control subjects. Some authors have reported a direct relationship between the presence of inflammatory cells and total viral load. However, more precise information on antibiotics or corticosteroid use is needed in order to be better able to link data on the inflammatory response with viral–bacterial load in COPD. There is evidence that infection by respiratory viruses could influence the bacterial microbiome. More than 60% of COPD patients experience a secondary bacterial infection after a rhinovirus infection. Viral infections may damage epithelial cells, which can facilitate the subsequent bacterial colonisation. Viral infections also suppress the activation of alveolar macrophages, inhibit neutrophil function and reduce cytotoxic activity and cytokine production of NK cells. Influenza virus infections are related to the suppression of the Th17 response during a secondary bacterial infection in mice. These data point to a link between bacterial–viral infections and the related immune response in stable and exacerbated COPD patients.

Other cell functions

Necroptosis and pyroptosis represent two pathways of genetically encoded lytic cell death. These two mechanisms of cell death, distinct from apoptosis, induce the release of a number of pro-inflammatory molecules, including damage-associated molecular patterns (DAMPs), IL-1β and IL-18, which can induce significant inflammatory and possibly auto-immune responses in the involved tissues. Necroptosis is dependent on a multiprotein complex formation called necrosome. Activation of death receptors or cytosolic sensing receptors may activate the necrosome with membrane association of MLKL causing plasma membrane damage and release of DAMPs and inflammatory cytokines. In cigarette smoke-exposed human bronchial epithelial cells, necroptosis markers are reported to be significantly increased. The canonical model of pyroptosis involves inflammasome (NLRP3) activation. Cellular stressors activate NLRP3, followed by activation of caspase-1 capable of inducing IL-1β and IL-18 activation through gasdermin pores. In turn, gasdermin pores promote the release of activated pro-inflammatory cytokines (IL-1β and IL-18) and DAMPs, increasing the pro-inflammatory effects of pyroptosis. The non-canonical pathway of pyroptosis involves caspase-4/5/11 resulting in the activation of gasdermin D. Dermatophagoides farinae-1 has been reported to induce human bronchial epithelial cell death by pyroptosis by increasing lactate dehydrogenase release in association to IL-1β release and caspase-1 activation. Interestingly, recently we did not find any NLRP3 activation/increase in the bronchial tissue and lung parenchyma of stable COPD patients (with different severity), and also we found no difference in the levels of IL-1β, IL-18 and caspase-1 of COPD patients compared to control groups. We did not measure the levels of pyroptosis in our bronchial tissue or BAL samples from COPD and control subjects. However, from these data, we can speculate that pyroptosis may act through non-canonical pathways in patients with stable COPD of different severity.

Conclusions

The immune responses in the lung of patients with COPD include both innate and adaptive inflammatory changes related to the chronic inhalation of cigarette smoke, oxidative stress markers and bacterial/viral infections. Data obtained from bronchial biopsies, lung tissue specimens, sputum and BAL samples comparing the lower airways of COPD patients of different severity with control subjects have provided novel insights into the pathogenetic role of the different inflammatory cells, inflammatory mediators and cytokines and intracellular signalling pathways, enhancing our knowledge of the immunology of stable and exacerbated COPD. The complex actions involving macrophages, dendritic cells, neutrophils, T-lymphocytes and structural cells which trigger innate and cell-mediated inflammatory responses, interacting with external bacterial/viral and oxidant challenges, are responsible for the clinical consequences of irreversible airflow limitation, lung remodelling and emphysema which develop in these patients. A better comprehension of the homeostatic or impaired inflammatory cell functions is also relevant in the pathogenesis of COPD. Understanding the dynamics of these inflammatory and structural changes in different clinical conditions and different phenotypes (*e.g.* prevalent airways disease *versus* prevalent emphysema, frequent exacerbators *versus* non-frequent exacerbators) of COPD patients will improve our knowledge of the pathologic and molecular mechanisms underlying COPD.

Further reading

- Berenson CS, *et al.* (2013). Phagocytic dysfunction of human alveolar macrophages and severity of chronic obstructive pulmonary disease. *J Infect Dis*; 208: 2036–2045.
- Bewley MA, *et al.* (2017). Impaired mitochondrial microbicidal responses in chronic obstructive pulmonary disease macrophages. *Am J Respir Crit Care Med*; 196:845–855.
- Cortez VS, *et al.* (2017). SMAD4 impedes the conversion of NK cells into ILC1-like cells by curtailing non-canonical TGF-β signaling. *Nat Immunol*; 18: 995–1003.
- Di Stefano A, *et al.* (2004). Cellular and molecular mechanisms in chronic obstructive pulmonary disease: an overview. *Clin Exp Allergy*; 34 :1156–1167.
- Di Stefano A, *et al.* (2009). T helper type 17-related cytokine expression is increased in the bronchial mucosa of stable chronic obstructive pulmonary disease patients. *Clin Exp Immunol*; 157: 316–324.
- Di Stefano A, *et al.* (2014). Innate immunity but not NLRP3 inflammasome activation correlates with severity of stable COPD. *Thorax*; 69: 516–524.
- Di Stefano A, *et al.* (2018). TGF-β signaling pathways in different compartments of the lower airways of patients with stable COPD. *Chest*; 153: 851–862.
- Eltboli O, *et al.* (2014). COPD exacerbation severity and frequency is associated with impaired macrophage efferocytosis of eosinophils. *BMC Pulm Med*; 14: 112.
- Frank D, *et al.* (2019). Pyroptosis *versus* necroptosis: similarities, differences, and crosstalk. *Cell Death Differ*; 26: 99–114.
- Guo H, *et al.* (2009). The functional impairment of natural killer cells during influenza virus infection. *Immunol Cell Biol*; 87: 579–589.
- Halwani R, *et al.* (2013). T helper 17 cells in airway diseases: from laboratory bench to bedside. *Chest*; 143: 494–501.
- Jones GW, *et al.* (2018). IL-27: a double agent in the IL-6 family. *Clin Exp Immunol*; 193: 37–46.
- Mackay AJ, *et al.* (2014). Detection and severity grading of COPD exacerbations using the exacerbations of chronic pulmonary disease tool (EXACT). *Eur Respir J*; 43: 735–744.
- Mjösberg J, *et al.* (2016). Human innate lymphoid cells. *J Allergy Clin Immunol*; 138: 1265–1276.
- Polverino F, *et al.* (2015). B cell-activating factor. An orchestrator of lymphoid follicles in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 192: 695–705.
- Sethi S, *et al.* (2002). New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*; 347: 465–471.
- Storisteanu DM, *et al.* (2017). Evasion of neutrophil extracellular traps by respiratory pathogens. *Am J Respir Cell Mol Biol*; 56: 423–431.
- Sze MA, *et al.* (2015). Host response to the lung microbiome in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 192: 438–445.
- Upham JW, *et al.* (2017). Dendritic cells in human lung disease: recent advances. *Chest*; 151: 668–673.
- Yamasaki K, *et al.* (2018). Lung macrophage phenotypes and functional responses: role in the pathogenesis of COPD. *Int J Mol Sci*; 19: E582.

Respiratory physiology

Susan A. Ward

The appropriateness of the ventilatory response to challenges such as hypoxia or altered metabolic rate depends on whether the pulmonary gas-exchange and acid–base requirements are achieved: *i.e.* $P_{\mathrm{aCO_2}}$, arterial pH ($\mathrm{pH_a}$) and $P_{\mathrm{aO_2}}$ within the relatively narrow range for optimal functioning. This involves a cascade of mechanisms: airflow and volume generation; pulmonary oxygen and carbon dioxide exchange; and control of ventilation (V'_{E}) with its associated respiratory perceptions. Each of these mechanisms can be adversely affected in pulmonary disease, with impaired respiratory-mechanical and gas-exchange function increasing the V'_{E} demands of the task and, in turn, the costs of meeting these demands in terms of respiratory-muscle work, perfusion and oxygen consumption.

Ventilatory requirements

Alveolar, and hence arterial, carbon dioxide and oxygen tensions ($P_{\mathrm{ACO_2}}$, $P_{\mathrm{aCO_2}}$, $P_{\mathrm{AO_2}}$, and $P_{\mathrm{aO_2}}$, respectively) can only be regulated if alveolar ventilation (V'_{A}) responds in an appropriate proportion to pulmonary carbon dioxide output ($V'_{\mathrm{CO_2}}$) and oxygen uptake ($V'_{\mathrm{O_2}}$), respectively. For carbon dioxide exchange (Fick's principle):

$$V'_{\mathrm{A}}=863\cdot V'_{\mathrm{CO_2}}/P_{\mathrm{ACO_2}} \tag{1}$$

where 863 is the constant that corrects for the different conditions of reporting gas volumes (*i.e.* standard temperature and pressure, dry for metabolic variables; body temperature and pressure, saturated for ventilatory variables) and the transformation of fractional concentration to gas tension.

Similarly, for oxygen:

$$V'_{\mathrm{A}}=863\cdot V'_{\mathrm{O_2}}/(P_{\mathrm{I^*O_2}}-P_{\mathrm{AO_2}}) \tag{2}$$

Key points

- The mechanical work of breathing comprises elastic (volume-related) and resistive (flow-related) components.
- With expiratory efforts causing intrapleural pressure (P_{IP}) to become positive, an equal pressure point (EPP) is created that results in expiratory flow limitation.
- Arterial hypoxaemia can result from alveolar hypoventilation, diffusion limitation, alveolar ventilation/perfusion (V'_{A}/Q') mismatch and/or right-to-left shunt. Only the latter three mechanisms also lead to a widened $P_{\mathrm{A\text{-}aO_2}}$ (*i.e.* inefficient pulmonary oxygen exchange).

where P_{IO_2} is inspiratory oxygen tension (P_{O_2}) and * is a relatively small correction factor (F_{AN_2}/F_{IN_2}, where F_{AN_2} and F_{IN_2} are the alveolar and inspiratory nitrogen fractions, respectively) that takes account of inspired ventilation normally being slightly greater than expired. This reflects the body's metabolic processes releasing less carbon dioxide relative to the oxygen used for a normal western diet, with a respiratory quotient (RQ=metabolic carbon dioxide production/metabolic oxygen consumption) of ~0.8.

As V'_A is common to equations 1 and 2, then:

$$(863 \cdot V'_{CO_2})/P_{ACO_2} \leftarrow V'_A \rightarrow (863 \cdot V'_{O_2})/(P_{I^*O_2} - P_{AO_2}) \tag{3}$$

If V'_{CO_2} and V'_{O_2} are equal (*i.e.* respiratory exchange ratio (R)=1), both P_{ACO_2} and P_{AO_2} can be regulated. However, both cannot be regulated if V'_{CO_2} and V'_{O_2} differ, *e.g.* when:

1) RQ changes as a result of dietary- or activity-related alterations in metabolic substrate utilisation; or

2) there are transient variations in body gas stores (particularly the carbon dioxide stores) as metabolic rate changes.

Under such conditions, V'_A changes in closer proportion to V'_{CO_2} than to V'_{O_2}, with P_{ACO_2} consequently being more closely regulated than P_{AO_2}; any resulting P_{aO_2} changes normally occur over the relatively flat region of the oxygen dissociation curve, such that arterial oxygen content (C_{aO_2}) is not greatly affected. However, the regulatory outcome is more complex, for example:

1) if significant arterial hypoxaemia develops, causing V'_A to increase out of proportion to V'_{CO_2} (hyperventilation) so as to constrain the fall in P_{aO_2}; or

2) with metabolic acid–base disturbances that evoke compensatory respiratory responses to ameliorate the pH_a change.

Importantly, it is the total V'_E, not V'_A, that is controlled to effect these regulatory functions. Substituting $V'_E \cdot (1-V_D/V_T)$ for V'_A in equation 1 (where V_D is the physiological dead space volume, V_T is tidal volume and V_D/V_T is the physiological dead space fraction of the breath), and assuming P_{ACO_2} to equal to P_{aCO_2} yields:

$$V'_E = (863 \cdot V'_{CO_2})/(P_{aCO_2} \cdot (1-V_D/V_T)) \tag{4}$$

Thus, the V'_E requirement is determined by P_{aCO_2}, V'_{CO_2} and V_D/V_T. Furthermore, the influence of metabolic acid–base disturbances can be accommodated by substituting P_{aCO_2} from equation 4 into the Henderson–Hasselbalch equation, *i.e.*

$$pH_a = pK' + \log([HCO_3^-]_a/\alpha \cdot P_{aCO_2}) \tag{5}$$

where $[HCO_3^-]_a$ is the arterial bicarbonate concentration and α is the carbon dioxide solubility coefficient relating P_{aCO_2} to carbon dioxide content. This yields:

$$pH_a = pK' + (\log([HCO_3^-]_a/25.6) \cdot (V'_E/V'_{CO_2}) \cdot (1-V_D/V_T)) \tag{6}$$

where $\log[HCO_3^-]_a/25.6$ represents the set point, V'_E/V'_{CO_2} the 'control' term and $(1-V_D/V_T)$ the pulmonary gas exchange efficiency.

Respiratory mechanics

A particular V'_E requirement can, in theory, be accomplished with an infinite combination of V_T and respiratory frequency (f_R). The V_T–f_R combination, in turn, influences the inspiratory-muscle pressure (P_{mus}) needed to effect inspiration:

$$P_{mus} = E \cdot V + R \cdot V' + I \cdot V'' \tag{7}$$

where V, V' and V'' are volume, air (and pulmonary tissue) flow and acceleration, and E, R and I are the pulmonary elastance, resistance and inertance, respectively. Normally, the inertance-related term makes an insignificant contribution, *i.e.* although the acceleration of the air can be large, its mass is small, and while the mass of the thorax is relatively large, its acceleration is small (*c.f.* conditions such as obesity having an abnormally increased thoracic mass). Practically, therefore, P_{mus} has static (volume-related, with no associated air flow) and resistive (flow-related) components.

The static component of P_{mus} equals the transpulmonary pressure (P_{tp}) required to effect a required degree of lung distension under static conditions, *i.e.* the 'distending' pressure:

$$P_{tp}=P_{alv}-P_{IP}=V/C_L \quad (8)$$

where P_{alv} and P_{IP} are alveolar and intrapleural pressures, respectively, and C_L is lung compliance. C_L is determined by the elastic properties of the lung parenchyma and the surface-active forces operating at the alveolar air–liquid interface, which are constrained by the influence of surfactant.

The normal static V–P_{tp} relationship (line 2 in figure 1) shows C_L to be largely independent of V over the tidal range but to decline as TLC is approached. When C_L is decreased (*e.g.* restrictive lung disease), a greater than normal increase in P_{tp} is required to effect a given lung inflation (line 1 in figure 1); an increased C_L (*e.g.* emphysema) requires a smaller P_{tp} increment (line 3 in figure 1). Also, as functional residual capacity (FRC) and the associated P_{IP} are determined by the magnitude of the opposing chest wall and lung recoil forces, FRC is smaller and P_{IP} more sub-atmospheric under conditions of increased recoil (line 1 in figure 1) than when recoil is reduced (line 3 in figure 1).

The resistive component of P_{mus} is the 'driving' pressure required to effect air flow, *i.e.* the difference between P_{alv} and pressure at the airway opening (atmospheric pressure (P_{atm})):

$$P_{alv}-P_{atm}=V'\cdot R=k_1\cdot V'+k_2\cdot V'^2 \quad (9)$$

The major site of this resistance lies in the segmental bronchi and larger-sized small bronchi. The bronchioles, although individually constituting sites of high resistance

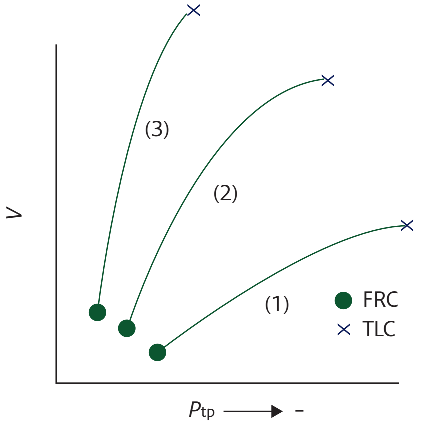


Figure 1. C_L curve between FRC and TLC for increased (1) and decreased (3) lung recoil relative to normal (2). The slope at any point represents C_L, i.e. change in V induced by change in P_{tp}.

because of their very small radius, collectively contribute relatively little to the overall resistance as they are very numerous (only ~10–20% of the airway resistance is related to airways <2 mm in diameter). The term $k_1 \cdot V'$ reflects the 'laminar' component of airflow, with $k_1=8\eta l/r^4$, where l is airway length, r is airway radius and η is gas viscosity. The term $k_2 \cdot V'^2$ reflects the 'turbulent' component, which imposes a greater demand on pressure generation because of the squaring of the V' term. Turbulent flow develops when the Reynolds number (R_e) exceeds a value of ~2000. As $R_e=V' \cdot 2r \cdot \rho/\eta$, where ρ is gas density, turbulent flow will predominate when V' is high, at branch points or across constricted regions. Hence, reducing ρ, for example by breathing high concentrations of helium instead of nitrogen (*i.e.* heliox), makes turbulence less likely.

Thoracic expansion during inspiration causes P_{alv} to become negative (*i.e.* below P_{atm}) and flow to occur, until the end of inspiration, when P_{alv} again equals P_{atm} (figure 2a and b). Thus, the pressure requirements for inspiratory flow and volume generation are reflected in P_{IP}: under static conditions, volume changes are simply related to changes in P_{IP} through the static C_L relationship (as P_{alv} is zero); while, during a normal inspiration, the additional muscular force needed to overcome R causes a greater negativity of P_{IP} at any given lung volume. The difference between the P_{IP} change needed to provide V' and that required to distend the lung statically is represented by the blue area in figure 2a and b, and is consequently greatest when V' is greatest. The respiratory-muscle work (W) performed in producing the inspiration can thus be calculated as: $\Delta V \cdot \Delta P_{IP}$ (figure 2c), where Δ represents a change, *i.e.* the sum of

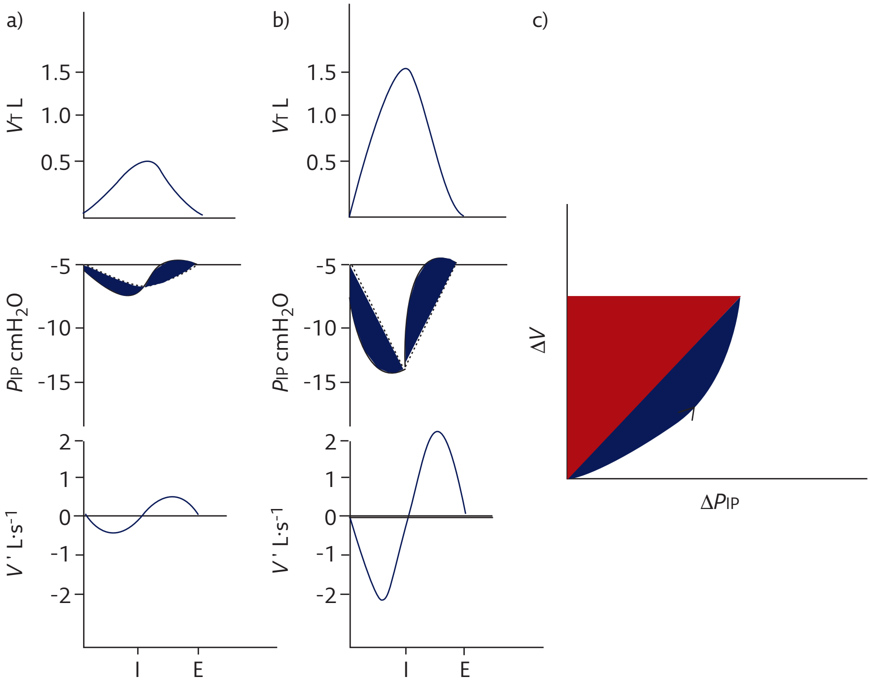


Figure 2. V_T, P_{IP} and V' changes for normal a) resting and b) exercising breaths. The dashed line on the P_{IP} curve represents the pressure needed to produce lung inflation statically. The blue area is the extra P_{IP} required to generate flow. c) Dynamic inspiratory V–P_{IP} curve. The red area represents the static inspiratory work of breathing; the blue area is the dynamic component. I: inspiration; E: expiration.

the elastic work required to overcome the static lung recoil forces (red area) and the resistive work (blue area). When breathing is stimulated (*e.g.* in exercise), the greater P_{alv} required to generate the increased V' amplifies the dynamic component of the V–P relationship (figure 2b), therefore increasing W. A similar effect is seen in patients with an abnormally increased R, a greater P_{alv} being required to achieve a particular V'. Expressing W relative to time yields the power output (W') of the inspiratory muscles that, when related to their oxygen consumption (Q'_{O_2}), allows considerations of respiratory muscle efficiency. It is only at very high levels of V'_{E} (*e.g.* at peak exercise in very fit endurance athletes) or when respiratory impedance is abnormally high (as in pulmonary disease) that W, W' and Q'_{O_2} can become significant and predispose to respiratory muscle fatigue.

When V'_{E} is low, expiration can be achieved entirely through the recoil pressure (P_{REC}) generated in the elastic structures of the lungs during the previous inspiration, *i.e.* providing the necessary driving pressure by increasing P_{alv} (figure 2a):

$$P_{\mathrm{tp}}=P_{\mathrm{REC}}=P_{\mathrm{alv}}-P_{\mathrm{IP}}=R\cdot V' \qquad (10)$$

The equality for P_{REC} deriving from equations 8 and 10 yields:

$$V/C_{\mathrm{L}}=R\cdot V' \qquad (11)$$

which can be rearranged as:

$$V'/V=1/R\cdot C_{\mathrm{L}} \qquad (12)$$

Flow at any point in expiration is thus determined by the interplay between lung volume, R and C_{L}. The term $R\cdot C_{\mathrm{L}}$ is the mechanical time constant (τ) of the respiratory system, with the unit of time, *i.e.* $(\mathrm{cmH_2O\cdot L^{-1}\cdot s})\cdot(\mathrm{L\cdot cmH_2O^{-1}})=\mathrm{s}$. Thus, if R or C_{L} (or both) are large, then V' will be low for a given lung volume. Complete passive emptying for a spontaneous expiration (*i.e.* down to FRC) requires expiratory duration to be sufficiently long (*i.e.* effectively $4\cdot\tau$ for an exponential process). With a normal τ of ~0.4 s (R and C_{L} being ~2 $\mathrm{cmH_2O\cdot L^{-1}\cdot s}$ and 0.2 $\mathrm{L\cdot cmH_2O^{-1}}$, respectively), this minimum period is ~1.6 s and translates to a total breath time (t_{tot}) of ~3 s, assuming an inspiratory duty cycle ($t_{\mathrm{I}}/t_{\mathrm{tot}}$, where t_{I} is inspiratory time) of ~0.45. Thus, if f_{R} exceeds ~20 $\mathrm{breaths\cdot min^{-1}}$, complete emptying requires expiratory flow to be augmented by expiratory muscle action; without this, end-expiratory lung volume will be greater than FRC. Such dynamic hyperinflation is a hallmark of the exercising COPD patient (figure 3b), where disease-related increases in R and/or C_{L} can lower this limiting f_{R} quite considerably.

That the maximal volitionally generated expiratory V' is greater at high than at low lung volumes (figure 3) is, of course, implicit in equation 11. That is, R and P_{REC} are each volume-dependent: at high volumes, R is relatively low reflecting a modest degree of airway distension (whose effect is amplified through the r^4 term), while P_{REC} is relatively high. Indeed, for a given τ, V' decreases as a linear function of V (equation 12), accounting for the descending limb of the maximal expiratory flow–volume curve normally being so linear (figure 3a).

In COPD, however, the lower maximal V' at TLC, despite the higher absolute lung volume (line 3 in figure 1), is indicative of an increased R and, for emphysema, a decreased P_{REC} (figure 3b), such that V' at a particular lung volume is lower than normal. In contrast, for restrictive lung disease, while maximal V' at TLC is low owing to poor distensibility (line 1 in figure 1), V' at a particular lung volume can even be slightly higher than normal owing to an increased P_{REC}. Furthermore, when there is regional nonuniformity of τ, as in COPD, for example, this can contribute to the typically ‘scooped’ maximal expiratory V' profile (figure 3b).

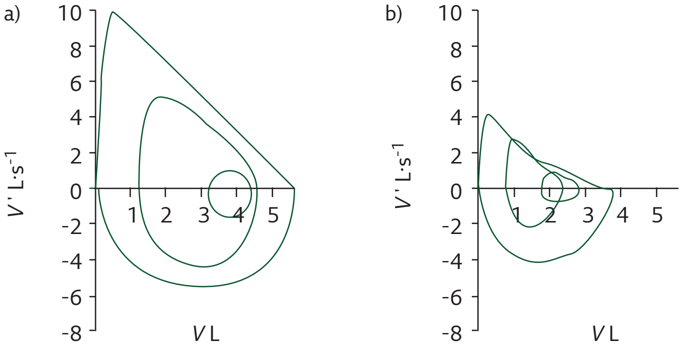


Figure 3. Inspiratory (downwards) and expiratory (upwards) flow–volume curves at rest, maximal exercise and with maximal volitional effort for a) a normal individual and b) a patient with COPD. Reproduced from Klas et al. *(1989), with permission from the publisher.*

The effects of P_{IP} on expiratory V' are not quite as straightforward, however, as those of R and P_{REC} (equation 10). P_{IP} is an index of the effort transmitted from the respiratory muscles to the lungs *via* the chest wall. During more forceful expirations, P_{IP} can become positive (*i.e.* supra-atmospheric), reflecting the chest wall volume decreasing faster than the lungs' intrinsic tendency to recoil. This results in a compressive force being applied to the intrapleural space. And as $P_{\text{alv}}=P_{\text{IP}}+P_{\text{REC}}$ (equation 10), P_{alv} will be more positive than P_{IP} by an amount equal to P_{REC}. As airway pressure (P_{aw}) declines from the supra-atmospheric alveolar value down to zero at the mouth as a result of frictional losses along the airways, a point will occur where P_{aw} becomes equal to P_{IP} resulting in the generation of an 'equal pressure point' (EPP) (*i.e.* at which the transmural pressure across the airway wall becomes zero) (figure 4).

The EPP becomes the limiting point for expiratory flow generation, with the maximum expiratory flow (V'_{max}) that can occur at a given lung volume and therefore P_{REC} being dictated as:

$$V'_{\text{max}}=P_{\text{REC}}/R_{\text{us}} \tag{13}$$

where R_{us} is the resistance of the upstream segment of the airways (between the alveolus and the EPP) (figure 4). Equation 13 explains why V'_{max} falls with decreasing

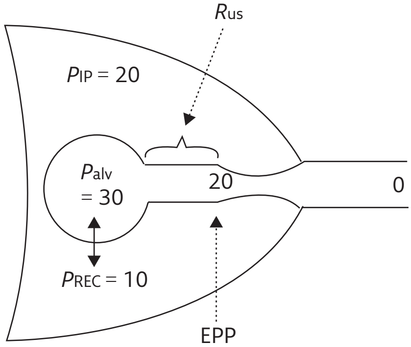


Figure 4. Airflow limitation in expiration. An EPP results when P*aw declines to a value equal to* P*REC. Values are expressed in cmH$_2$O.*

lung volume (*i.e.* P_{REC} decreases) and why, despite progressively greater expiratory efforts that result in a progressively more positive P_{IP}, V'_{max} at a given lung volume is not increased (effort-independence).

In normal individuals, the EPP occurs in the large airways (lower trachea or main stem bronchi), which, despite their tendency to become compressed, are prevented from completely collapsing by their cartilaginous support. With loss of lung recoil and/or increases in small airway resistance, however, the EPP migrates upstream. If it encroaches into the small unsupported airways, airways collapse occurs, with profound effects on V'_{max} (equation 13).

Pulmonary gas exchange

The effectiveness of pulmonary oxygen exchange is conventionally judged by the magnitude of the alveolar–arterial oxygen tension difference (P_{A-aO_2}), where P_{AO_2} is the value for the 'ideal lung' (*i.e.* one that hypothetically has no V'_A/perfusion (Q') heterogeneity and operates at the same R value as that of the actual lung). The ideal P_{AO_2} thus circumvents the difficulty of providing a single representative value for P_{AO_2} when there are regional variations in gas-exchange efficiency. It can be derived by re-arranging and amalgamating equations 1 and 2:

$$V'_{CO_2}/V'_{O_2}=R=(V'_A\cdot((P_{IO_2}\cdot F_{AN_2}/F_{IN_2})-P_{AO_2}))/(V'_A\cdot P_{ACO_2}) \tag{14}$$

$$P_{AO_2}=P_{IO_2}-P_{aCO_2}/R+(P_{aCO_2}\cdot F_{IO_2}\cdot(1-R)/R) \tag{15}$$

where F_{IO_2} is the inspiratory oxygen fraction. It is common practice to neglect the term $P_{aCO_2}\cdot F_{IO_2}\cdot(1-R)/R$, as it is zero when $R=1$ and only contributes a few mmHg or so when $R\neq1$. Therefore:

$$P_{AO_2}=P_{IO_2}-P_{aCO_2}/R \tag{16}$$

Impairments of pulmonary gas exchange typically result in arterial hypoxaemia and, in some instances, arterial hypercapnia. Six mechanisms can be identified as independent causes of arterial hypoxaemia: three of these affect P_{AO_2} (ambient hypoxia as with ascent to altitude, reduced RQ and alveolar hypoventilation) and three affect P_{A-aO_2} (diffusion limitation, increased right-to-left shunt and V'_A/Q' maldistribution).

Reduced RQ

Recalling that V'_E operates to regulate P_{aCO_2} by responding in a proportional fashion to V'_{CO_2}, when the RQ of the dietary substrate is reduced (*i.e.* by ingestion of a high-fat diet), the associated reduction in metabolic carbon dioxide production requires less ventilation to maintain a stable P_{aCO_2} (equation 3). This leads to hypoventilation relative to oxygen, *i.e.* V'_E is normal relative to V'_{CO_2}, but low relative to V'_{O_2}. Thus, P_{AO_2} and P_{aO_2} will fall.

Alveolar hypoventilation

This can occur in diseases or with drugs that affect the medullary respiratory-integrating centres or respiratory neuromuscular function, thus reducing the level of respiratory motor output. It may also be seen in severe COPD, consequent to increased small airway resistance and a high resistive work of breathing. Arterial hypoxaemia and hypercapnia result (equations 2 and 1, respectively), with the fall of P_{AO_2} being related to the rise of P_{ACO_2} through R (equation 16). When $R=1$, the increase in P_{ACO_2} and fall in P_{AO_2} that result from a reduction in V'_A are equal, as notionally are the corresponding changes in P_{aCO_2} and P_{aO_2}. However, as R is normally ~0.8 at rest, for each 10 mmHg (1.33 kPa) decrease in P_{aO_2} that results from a fall of V'_A, P_{aCO_2} will increase by only 8 mmHg (1.06 kPa). It should be noted that the hypoxaemia can be offset by administration of supplementary oxygen.

Diffusion impairment

Fick's law indicates that impairments in the pulmonary diffusive flux of oxygen (or carbon dioxide) can result from:

1) a reduction in the driving pressure (for oxygen, $\Delta P\mathrm{O}_2$),

2) a reduction in the available surface area for diffusion (A), and/or

3) an increased path length for diffusion (l):

$$V'\mathrm{O}_2=A/l\cdot d\cdot\Delta P\mathrm{O}_2 \qquad (17)$$

where d, the diffusion coefficient for oxygen, is inversely proportional to gas molecular weight (MW) in the gas phase (d=1/√MW), and directly proportional also to gas solubility (s) in the blood phase (d=s/√MW). Hence, as oxygen is lighter than carbon dioxide, it diffuses 18% more rapidly in the gas phase for the same gas tension gradient. In the blood phase, however, carbon dioxide is 20 times more diffusible than oxygen, owing to its greater solubility.

During inspiration, oxygen is transported down the tracheobronchial tree by convective or bulk flow. At the level of the alveolar ducts, owing to the large overall cross-sectional area of the airways and the resulting reduction in linear velocity of the inspired gas, further movement to the alveolar–capillary membrane relies on diffusion. Diffusion through the alveolar gas space does not normally limit oxygen transfer into pulmonary capillary blood. Thus, as the average alveolar diameter is normally only ~200 µm, diffusion equilibrium (*i.e.* $\Delta P\mathrm{O}_2$=0) throughout the alveolus is attained rapidly: this is normally 80% complete within ~0.002 s, which is several orders of magnitude less than the time for which pulmonary capillary blood is exposed to the alveolar gas-exchange surface (*i.e.* the pulmonary–capillary transit time ($t\mathrm{TR}$), ~0.8 s at rest). In conditions such as emphysema, air-sac enlargement increases intra-alveolar diffusion distances, predisposing to less efficient oxygen (and carbon dioxide) exchange.

More commonly, however, diffusion limitation reflects exchange impairments between alveolar gas and pulmonary capillary blood. The rate of diffusive uptake of oxygen into blood is given by:

$$V'\mathrm{O}_2=A/l\cdot d\cdot(P\mathrm{AO}_2-P\mathrm{cO}_2) \qquad (18)$$

where A is the alveolar surface area in contact with perfused pulmonary capillaries; l is the diffusion path length between the alveolar surface fluid lining and the erythrocyte interior that comprises alveolar epithelium, interstitial space, capillary endothelial cells, plasma, erythrocyte cell membrane and, for a reactive gas species such as oxygen, its chemical combination with haemoglobin; and $P\mathrm{cO}_2$ is mean pulmonary capillary $P\mathrm{O}_2$. It is conventional to combine A, l and d into a single term, the transfer factor of the lung for oxygen ($T\mathrm{LO}_2$):

$$V'\mathrm{O}_2=T\mathrm{LO}_2\cdot(P\mathrm{AO}_2-P\mathrm{cO}_2) \qquad (19)$$

$T\mathrm{LO}_2$ can be usefully subdivided into its functional components: the 'membrane' component ($T\mathrm{MO}_2$) and that due to chemical combination:

$$1/T\mathrm{LO}_2=1/T\mathrm{MO}_2+1/\theta\cdot V\mathrm{c} \qquad (20)$$

where θ is the reaction rate coefficient for chemical combination of oxygen with haemoglobin and $V\mathrm{c}$ is pulmonary capillary blood volume. Because of technical limitations associated with estimating $P_{\mathrm{cO_2}}$, it is conventional to determine transfer factors of the lung and membrane for carbon monoxide (T_{LCO} and T_{MCO}, respectively), as the high affinity of haemoglobin for carbon monoxide ensures that the pulmonary capillary carbon monoxide tension (P_{cCO}) is effectively zero, despite its inspired tension being caused to be elevated during the procedure.

The initial driving pressure across the alveolar–capillary membrane (*i.e.* at the entrance to the capillary bed) is given by the difference between $P_{\mathrm{AO_2}}$ (normally ~100 mmHg (~13.3 kPa)) and mixed venous $P_{\mathrm{O_2}}$ ($P_{\mathrm{vO_2}}$) (normally ~40 mmHg (~5.3 kPa) at rest, and decreasing in exercise). As the blood traverses the pulmonary capillary bed, the rate at which oxygen is taken up declines, reflecting the progressive reduction in driving pressure as capillary $P_{\mathrm{O_2}}$ rises. Diffusion equilibrium is normally reached within 0.25–0.3 s (*i.e.* well before blood reaches the end of the capillary); thus, pulmonary end-capillary $P_{\mathrm{O_2}}$ ($P_{\mathrm{c'O_2}}$)=$P_{\mathrm{AO_2}}$. This large safety margin becomes compromised, however, when t_{TR} is shortened to such a degree that there is insufficient time for the attainment of diffusion equilibrium, *i.e.* $P_{\mathrm{c'O_2}}<P_{\mathrm{AO_2}}$. As $t_{\mathrm{TR}}=V_{\mathrm{c}}/Q'$, an increase in Q' (*e.g.* high-intensity exercise) can compromise diffusion equilibrium, resulting in arterial hypoxaemia. However, the decrease in t_{TR} with increases in Q' is less than expected, because the capillary blood volume (Q_{c}) actually increases with Q', consequent to distension of already-perfused capillaries and recruitment of previously unperfused capillaries; this serves to protect against diffusion disequilibrium.

A lowered $P_{\mathrm{AO_2}}$, as occurs with ascent to high altitude, when an individual breathes hypoxic inspirate or with hypoventilation, slows the rise of pulmonary capillary $P_{\mathrm{O_2}}$. This is because the initial driving pressure ($P_{\mathrm{AO_2}}$–$P_{\mathrm{vO_2}}$) is smaller, as the operating slope of the oxygen dissociation curve (β) is steeper, such that the arteriovenous oxygen content difference expresses a smaller arteriovenous $P_{\mathrm{O_2}}$ difference.

A useful expression relating to the interplay of factors that dictate whether or not diffusion equilibrium will actually be attained (*i.e.* whether $P_{\mathrm{c'O_2}}=P_{\mathrm{AO_2}}$) is:

$$(P_{\mathrm{AO_2}}-P_{\mathrm{c'O_2}})/(P_{\mathrm{AO_2}}-P_{\mathrm{vO_2}})=e^{-T_{\mathrm{LO_2}}/Q'\cdot\beta} \qquad (21)$$

where the term $T_{\mathrm{LO_2}}/Q'\cdot\beta$ reflects the ratio of diffusive conductance ($T_{\mathrm{LO_2}}$) to perfusive conductance ($Q'\cdot\beta$). Diffusion equilibrium is less likely to be attained if $T_{\mathrm{LO_2}}$ is low and/or Q' and β are high. For example, an increased path length (*e.g.* alveolar proteinosis or pulmonary oedema) and/or a reduced surface area for exchange (*e.g.* pulmonary embolism or restrictive lung disease) slow the diffusive flux of oxygen because of their effects on $T_{\mathrm{LO_2}}$. With very high levels of Q' (*e.g.* very fit endurance athletes exercising at or close to maximum) or very high linear capillary-blood velocities (*e.g.* pulmonary embolism, where there are fewer participating capillaries), the reduction in t_{TR} can lead to a widened $P_{\mathrm{A\text{-}aO_2}}$ and arterial hypoxaemia. Supplemental oxygen can, through its effects on $P_{\mathrm{AO_2}}$ and therefore driving pressure, speed the rise of pulmonary capillary $P_{\mathrm{O_2}}$ and thus ameliorate the degree of gas-exchange impairment.

However, although severe degrees of arterial hypoxaemia can result from diffusion impairment, carbon dioxide retention is rarely a problem. This is because any increase in $P_{\mathrm{aCO_2}}$ that might occur tends to be corrected by ventilatory control mechanisms, which are considered to be exquisitely sensitive to carbon dioxide (*i.e.* central and carotid body chemoreflexes); in contrast, hypoxic ventilatory stimulation only becomes appreciable when $P_{\mathrm{aO_2}}$ falls below ~60 mmHg (~7.98 kPa). Hence, moderate diffusion impairment is accompanied by a decreased $P_{\mathrm{aO_2}}$, a widened $P_{\mathrm{A\text{-}aO_2}}$ and a relatively normal $P_{\mathrm{aCO_2}}$; with more severe impairment, predisposing to hypoxic ventilatory stimulation, there will be a more marked arterial hypoxaemia, greater widening of the $P_{\mathrm{A\text{-}aO_2}}$ and a low $P_{\mathrm{aCO_2}}$.

Right-to-left shunt

A right-to-left shunt (Q'_s) occurs when venous blood bypasses the pulmonary capillary bed, thus providing a degree of venous admixture with blood from exchanging alveolar units. It normally reflects venous drainage from the larger airways (which enters the pulmonary veins) and from coronary vessels (which enters the left ventricles *via* the Thebesian veins). This represents only a small percentage of Q' and, therefore, amounts to a reduction in P_{aO_2} of only a few mmHg below $P_{c'O_2}$. However, Q'_s/Q' can be markedly increased in congenital heart disease (*e.g.* atrial or ventricular septal defects, and pulmonary arteriovenous fistulae), leading to significant arterial hypoxaemia and widening of the P_{A-aO_2}.

The Q'_s/Q' relationship derives from the recognition that the rate of oxygen delivery into the systemic arterial circulation can be viewed as being made up of an homogeneous 'ideal' pulmonary capillary component and a 'pure' shunt component. Reverting again to the Fick principle, but now for the 'blood' side, and using the simple equality $Q'=Q'_c+Q'_s$:

$$Q' \cdot C_{aO_2} = Q'_c \cdot C_{c'O_2} + Q'_s \cdot C_{vO_2} \qquad (22)$$

where $C_{c'O_2}$ is the end-capillary oxygen content and C_{vO_2} is the mixed-venous oxygen content. This rearranges to yield:

$$Q'_s/Q' = (C_{c'O_2} - C_{aO_2})/(C_{c'O_2} - C_{vO_2}) \qquad (23)$$

C_{aO_2} and C_{vO_2} can be measured directly from blood samples, while $C_{c'O_2}$ is derived through the standard oxygen dissociation curve, assuming $P_{c'O_2}$ equals the ideal P_{AO_2} (equation 16). It should be noted that this equation also assumes that all the shunted blood is of mixed-venous composition, which may not necessarily be the case for bronchial venous blood. This estimate of Q'_s/Q' thus provides an overestimate of the true shunt, as it incorporates a fraction of the perfusion draining from alveolar units having poorly exchanging capillaries (with low V'_A/Q' values), *i.e.* creating a 'shunt-like' effect.

A right-to-left shunt must therefore result in arterial hypoxaemia, *i.e.* even a small contribution from non-arterialised blood will depress the resulting C_{aO_2}, owing to the nonlinearity of the oxygen dissociation curve. The severity of the hypoxaemia will depend both on Q'_s/Q' and C_{vO_2}, being more marked when the former is larger and the latter is lower. A hallmark feature of a pure right-to-left shunt is that the elevation of P_{aO_2} in response to administration of 100% oxygen is appreciably less than expected. This is because the shunt flow cannot 'see' the elevated P_{AO_2} in the exchanging alveoli, and also that further increases in P_{AO_2} will have little effect on $C_{c'O_2}$ because the blood is already essentially fully saturated; it is only the dissolved component of the oxygen content that can be increased, and this will be relatively small because of the low solubility of oxygen in plasma.

A right-to-left shunt also has the potential to cause carbon dioxide retention, but this is rarely observed owing to the normally small mixed venous-to-arterial P_{CO_2} difference (~6 mmHg (~0.8 kPa) at rest *versus* ~60 mmHg (~7.98 kPa) for oxygen) and also the mechanisms of ventilatory control that normally restore an increased P_{aCO_2} to normal (see earlier). Again, however, should P_{aO_2} fall sufficiently to cause hypoxic stimulation of the carotid chemoreceptors, then P_{aCO_2} will fall; but, without this, P_{aCO_2} would rise. Thus, a moderate right-to-left shunt leads to a reduced P_{aO_2} and a widened P_{A-aO_2}, but a relatively normal P_{aCO_2}. Severe right-to-left shunts cause a markedly reduced P_{aO_2} and a markedly widened P_{A-aO_2}, with the possibility of a lowered P_{aCO_2}.

V'_A/Q' maldistribution

Although overall V'_A may be approximately equal to overall Q' in the lung, there may nonetheless be regions with high, normal and low V'_A/Q' ratios. This has important implications for regional alveolar gas and pulmonary end-capillary blood composition, and therefore for overall arterial blood-gas status. That is, gas and blood from low V'_A/Q' regions will reflect hypoventilation (*i.e.* low P_{O_2} and high P_{CO_2}) and, in the extreme, alveolar shunt ($V'_A/Q'=0$) (see earlier); gas and blood from normal V'_A/Q' regions will have a normal P_{O_2} and P_{CO_2}; and gas and blood from high V'_A/Q' regions will reflect hyperventilation (*i.e.* high P_{O_2} and low P_{CO_2}) and, in the extreme, alveolar dead space ($V'_A/Q'=\infty$).

An analogous formulation to that for estimation of Q'_s/Q' can be applied to the estimation of V_D/V_T (recalling that V_D reflects the sum of the anatomical and alveolar dead spaces). That is, the assumption is made that the volume of carbon dioxide cleared in exhalation originates solely from a homogeneous exchanging alveolar compartment (Bohr technique):

$$V_T \cdot F_{ECO_2} = V_A \cdot F_{ACO_2} \tag{24}$$

where F_{ECO_2} and F_{ACO_2} are the mixed expired and alveolar carbon dioxide fractions and V_A is the volume of exchanging alveoli. Substituting V_T-V_D for V_A, converting fractional concentrations to gas tensions, making the reasonable assumption that $P_{ACO_2}=P_{aCO_2}$ (attributable to Enghoff) and rearranging yields:

$$V_D/V_T = (P_{aCO_2}-P_{ECO_2})/P_{aCO_2} \tag{25}$$

Even in the normal lung, there is evidence of mild V'_A/Q' mismatch. Owing to the influence of gravity, Q' is distributed preferentially to the dependent regions of the lung (*i.e.* towards the base in the upright posture). A similar, gravitationally induced effect is also seen for V'_A, although its magnitude is less striking. Thus, the alveoli in the dependent regions of the lung are smaller, as the hydrostatic pressure in the surrounding interstitium is greater. They are therefore constrained to operate over the lower, steeper portion of the C_L curve, in contrast to the larger apical units. Thus, the smaller basal units undergo a greater expansion for a given increase of P_{TP} during inspiration and are therefore better ventilated than the apical units. Despite this, the apical units have a relatively high V'_A/Q' while the basal units have a relatively low V'_A/Q'; *i.e.* reflecting the larger apical-to-base difference in Q'. Naturally, the degree of V'_A/Q' mismatch is considerably greater in many pulmonary disease states (*e.g.* COPD, diffuse interstitial fibrosis and pulmonary vascular occlusive disease) and its topographical location is not predictable.

The overall (or mean) P_{AO_2} and P_{ACO_2} result from an averaging of the respective gas concentrations from each individual alveolar gas 'stream', in proportion to the local V'_A. Likewise, the overall (or mean) P_{aO_2} and P_{aCO_2} will result from a Q'-weighted averaging of the respective gas contents from each individual pulmonary capillary 'stream'. However, it is important to recognise that the shape of the oxygen and carbon dioxide dissociation curves also have to be taken into account in order to derive these P_{aO_2} and P_{aCO_2} values (figure 5).

Owing to the sigmoid shape of the oxygen dissociation curve, low V'_A/Q' regions lead both to low P_{O_2} and low oxygen content in pulmonary end-capillary blood; in contrast, while high V'_A/Q' regions lead to a high $P_{c'O_2}$, $C_{c'O_2}$ is only slightly increased above the normal value because the oxygen dissociation curve is relatively flat in this range (figure 5). Mixing blood from low V'_A/Q' regions with blood from high V'_A/Q' regions

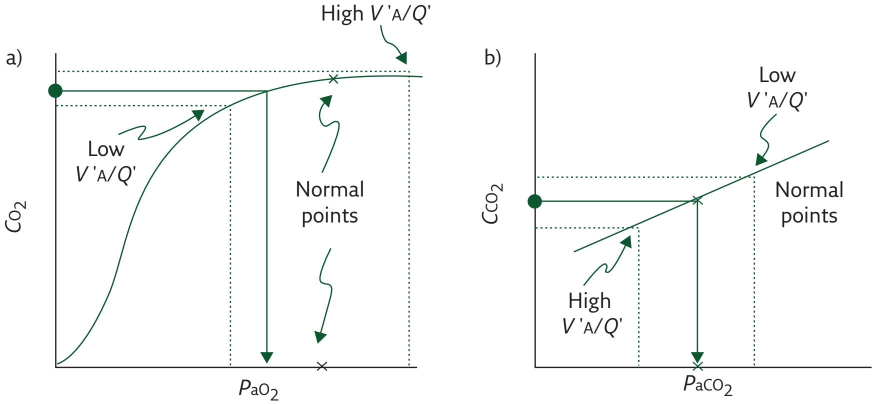


Figure 5. Influence of altered V′A/Q′ *on mean* P_{aO_2} *and* P_{aCO_2}. *a) The sigmoid oxygen dissociation curve leads to arterial hypoxaemia (solid vertical arrow) compared with 'normal' (×). b) This effect is not evident for carbon dioxide, because the carbon dioxide dissociation curve is relatively linear over the physiological range. Reproduced from Whipp (2002), with permission from the publisher.*

will therefore result in a mean P_{aO_2} that is weighted towards low *V′*A/*Q′* blood values (figure 5). P_{aO_2} will also depend on the volumes of blood from each region contributing to the mixed arterial blood. Thus, the high *V′*A/*Q′* regions (even if haemoglobin is completely saturated) are unable to compensate for the low *V′*A/*Q′* regions, as their perfusion is usually less. Consequently, even though the overall *V′*A/*Q′* may be normal, *V′*A/*Q′* mismatch results in arterial hypoxaemia, with mean P_{aO_2} being lower than the actual mean P_{AO_2} or its 'ideal' representation; *i.e.* P_{A-aO_2} is widened.

In contrast, the carbon dioxide dissociation curve is essentially linear in the physiological range (figure 5). This therefore allows the hyperventilatory effects of the high *V′*A/*Q′* regions to better counterbalance the hypoventilatory effects of the low *V′*A/*Q′* regions on the resulting mean P_{aCO_2} (figure 5). It should be noted, however, that the high *V′*A/*Q′* regions exert a proportionally greater influence on mean P_{ACO_2} than do the low *V′*A/*Q′* regions. Hence, with appreciable *V′*A/*Q′* disturbances, $P_{ACO_2}<P_{aCO_2}$.

The pattern of arterial blood and alveolar gas tensions in *V′*A/*Q′* mismatch is such that with mild or moderate mismatch, P_{aO_2} is low, P_{A-aO_2} is widened, with P_{aCO_2} being normal or low depending on the degree of ventilatory stimulation consequent to the hypoxaemia. In severe *V′*A/*Q′* impairment associated with severe airway obstruction, hypoventilation can ensue owing to the increased work of breathing and, therefore, cause an increased P_{aCO_2}. This, of course, reduces P_{aO_2} even more.

Further reading

- D'Angelo E (1999). Dynamics. *In:* Milic-Emili J, ed. Respiratory Mechanics (ERS Monograph). Sheffield, European Respiratory Society; pp. 54–67.
- Farhi LE (1986). Ventilation–perfusion relationships. *In:* Farhi LE, *et al.*, eds. Handbook of Physiology. The Respiratory System, Mechanics of Breathing, vol. IV. Bethesda, American Physiological Society; pp. 199–215.

- Hsia CC, *et al.* (2016). Lung structure and the intrinsic challenges of gas exchange. *Compr Physiol*; 6: 827–895.
- Hughes JMB (2005). Pulmonary gas exchange. *In:* Gosselink R, Stam H, eds. Lung Function Testing (ERS Monograph). Sheffield, European Respiratory Society; pp. 106–126.
- Klas JV, *et al.* (1989). Voluntary *versus* reflex regulation of maximal exercise flow: volume loops. *Am Rev Respir Dis*; 139: 150–156.
- Lindinger MI, *et al.* (2012). Effects of gas exchange on acid-base balance. *Compr Physiol;* 2: 2203–2254.
- Lumb AB (2016). Nunn's Applied Respiratory Physiology. 8th Edn. London, Elsevier.
- Maina JN, *et al.* (2005). Thin and strong! The bioengineering dilemma in the structural and functional design of the blood–gas barrier. *Physiol Rev*; 85: 811–844.
- Mead J, *et al.* (1964). Dynamics of breathing. *In*: Fenn WO, *et al.*, eds. Handbook of Physiology, Respiration, vol. 1. Washington, American Physiological Society; pp. 411–427.
- Otis AB (1964). The work of breathing. *In*: Fenn WO, *et al.*, eds. Handbook of Physiology, Respiration, vol. 1. Washington, American Physiological Society; pp. 592–607.
- Piiper J (2000). Perfusion, diffusion and their heterogeneities limiting blood-tissue O_2 transfer in muscle. *Acta Physiol Scand*; 168: 603–607.
- Pride NB, *et al.* (1986). Lung mechanics in disease. *In*: Macklem PT, *et al.*, eds. Handbook of Physiology. The Respiratory System, Mechanics of Breathing, vol. III, part 2. Bethesda, American Physiological Society; pp. 659–692.
- Rahn H (1949). A concept of mean alveolar air and the ventilation–blood flow relationships during pulmonary gas exchange. *Am J Physiol*; 158: 21–30.
- Riley RL, *et al.* (1949). 'Ideal' alveolar air and the analysis of ventilation–perfusion relationships in the lung. *J Appl Physiol*; 1: 825–847.
- Rodarte JR, *et al.* (1986). Dynamics of respiration. *In*: Macklem PT, *et al.*, eds. Handbook of Physiology. The Respiratory System, Mechanics of Breathing, vol. III, part 1. Bethesda, American Physiological Society; pp. 131–144.
- Sieck GC, *et al.* (2013). Mechanical properties of respiratory muscles. *Compr Physiol*; 3: 1553–1567.
- Weibel ER (1984). Pathway for Oxygen. Cambridge, Harvard University Press.
- West JB (1990). Ventilation/Blood Flow and Gas Exchange. Oxford, Wiley-Blackwell.
- West JB, *et al.* (1997). Ventilation–perfusion relationships. *In*: Crystal RG, *et al.*, eds. The Lung: Scientific Foundations. 2nd Edn. Philadelphia, Lippincott-Raven Publishers; pp. 1693–1709.
- Whipp BJ (2002). The physiology and pathophysiology of gas exchange. *In*: Bittar EE, ed. Pulmonary Biology in Health and Disease. New York, Springer-Verlag; pp. 189–217.
- Zavorsky GS (2003). Red cell pulmonary transit times through the healthy human lung. *Exp Physiol*; 88: 191–200.

Control of ventilation

Brian J. Whipp† and Susan A. Ward

The ventilatory control system is highly complex, involving:

- transmission of primary humoral stimuli from their sites of generation to sensing elements;
- processing of chemoreceptor afferent activity within brainstem respiratory integrating regions;
- production of respiratory motor-discharge patterns;
- neuromuscular transmission at the respiratory muscles; and
- generation of appropriate pulmonary pressure gradients to produce the required airflow and ventilation.

Consequently, while inhalation of hypercapnic or hypoxic gas mixtures, either individually or in combination, is widely used to assess the normalcy of ventilatory chemoreceptor sensitivity, interpretation of responses should be made in the context of the entire 'input–output' relationship. Individuals with increased airway resistance or impaired respiratory muscle function, for example, may have

Key points

- Ventilatory carbon dioxide responsiveness is determined as the slope of the linear iso-oxic V'_E–P_{ETCO_2} relationship ($\Delta V'_E/\Delta P_{ETCO_2}$), using steady-state, constant-concentration inspirates or hyperoxic rebreathing.
- $\Delta V'_E/\Delta P_{ETCO_2}$ reflects central and, if P_{aO_2} is not excessive, also carotid chemoreceptor activity. Being appreciably shorter, the rebeathing test is preferred although $\Delta V'_E/\Delta P_{ETCO_2}$ reflects only central chemoreflex activity.
- Ventilatory hypoxic responsiveness is determined from the curvilinear isocapnic V'_E–P_{ETO_2} response, using steady-state, constant-concentration inspirates or rebreathing. It reflects solely carotid chemoreceptor activity.
- Expressing V'_E *versus* S_{aO_2} linearises the profile, with the slope ($\Delta V'_E/\Delta S_{aO_2}$) providing the hypoxic responsiveness index (however, P_{O_2}, not S_{O_2}, is the actual stimulus). An alternative approach is the Dejours hypoxia-withdrawal test: abrupt oxygen administration from a prior hypoxic background acutely suppresses carotid body activity to cause a transient, rapid V'_E decline; the maximum decrease as a fraction of the total hypoxic V'_E provides the index of ventilatory hypoxic responsiveness.

an abnormally low overall ventilatory carbon dioxide or hypoxic response despite normal chemoreceptor function.

Ventilatory response to inhaled carbon dioxide

The relationship between ventilation (V'_E) and arterial (a) or alveolar (A; often represented by end-tidal (ET)) carbon dioxide tension (P_{CO_2}), for an individual acutely inhaling a series of increasingly hypercapnic inspirates (*e.g.* in the range 3–6%), each for sufficiently long to establish a steady state, is used to estimate overall ventilatory carbon dioxide responsiveness. The resulting V'_E–P_{ETCO_2} relationship is typically linear in healthy normoxic individuals, with a slope ($\Delta V'_E/\Delta P_{ETCO_2}$) averaging ~2–3 $L \cdot min^{-1} \cdot mmHg^{-1}$. $\Delta V'_E/\Delta P_{ETCO_2}$ may increase slightly in the higher P_{ETCO_2} range when breathing pattern transitions from largely tidal volume mediation towards breathing frequency; in such instances, ventilatory carbon dioxide responsiveness is normally ascribed to the lower slope value. $\Delta V'_E/\Delta P_{ETCO_2}$ is primarily determined by the carbon dioxide responsiveness of the central 'chemoreceptors'. Traditionally these were localised to the ventral medullary surfaces, but more recently foci such as the retrotrapezoid nucleus, the caudal nucleus tractus solitarius, the locus coeruleus, the pre-Bötzinger complex and medullary raphe nuclei have also been identified. The neuronal substrate underlying central CO_2–H^+ chemoreception has been proposed to include pH-regulated and Kir transport potassium channels.

If P_{aO_2} is not excessive, the peripheral chemoreceptors (predominantly, if not exclusively, the carotid bodies in humans) also contribute to ventilatory carbon dioxide responsiveness. For example, at P_{aO_2} levels of ~90 mmHg, the central component accounts for 70–75% of the response, with the peripheral (carotid body) component accounting for the remainder. However, as the carotid body component of carbon dioxide responsiveness increases with reductions of P_{aO_2} below normal, $\Delta V'_E/\Delta P_{ETCO_2}$ increases with greater, constant degrees of hypoxaemia and decreases with greater, constant degrees of hyperoxia. This results in a 'fan' of hypoxia-dependent ventilatory carbon dioxide response slopes reflecting the additive 'sensitivity' (also termed 'potentiation') between carotid body and central response components, but with little or no change in the extrapolated V'_E intercept on the P_{CO_2} axis (figure 1). By contrast, an imposed metabolic acidaemia or alkalaemia results in a parallel shift of the V'_E–P_{ETCO_2} relationship (*i.e.* no change in ventilatory carbon dioxide responsiveness) with a reduced or increased V'_E intercept, respectively.

The increasing $\Delta V'_E/\Delta P_{ETCO_2}$ with greater levels of simultaneous hypoxia reflects a progressively greater carotid body response component; it is crucial, therefore, to maintain P_{aO_2} constant (iso-oxic) during the CO_2 inhalation test. Above a P_{aO_2} of ~200 mmHg, the carotid body component is effectively inactivated in humans and hence the sufficiently hyperoxic carbon dioxide response entirely reflects that of the central component. Interpretation depends on the relationships between the typically measured P_{ETCO_2} (or, less typically, P_{aCO_2}) and P_{CO_2} (and hydrogen ion concentration $[H^+]$) at each set of chemoreceptors; these relationships depend on factors such as the local tissue perfusion, carbon dioxide production, carbon dioxide capacitance, H^+ buffering capacity and metabolic rate. Thus, the carbon dioxide equilibration process is rapid at the carotid body chemoreceptors, but is considerably delayed at sites of central chemoreception. Furthermore, one must be careful to assume that hypoxia does not influence central chemoreceptor responsiveness. It has the potential to do this indirectly, for example, by increasing cerebral blood flow. The consequent carbon dioxide wash-out lowers local tissue P_{CO_2} and also narrows the difference between it and P_{aCO_2}.

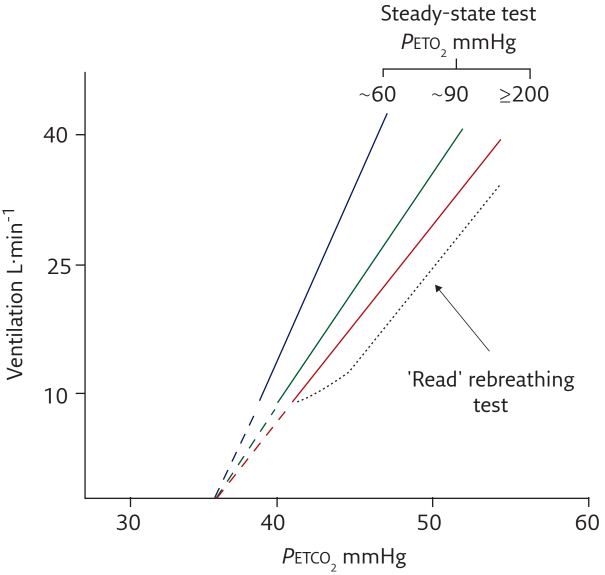


Figure 1. Steady-state ventilatory responses to inhaled P_{CO_2} at constant end-tidal oxygen tension (P_{ETO_2}; solid lines). The dotted line depicts the response to progressively increasing P_{CO_2} (Read's hyperoxic CO_2 rebreathing test).

Three or more levels of inspired P_{CO_2} (P_{ICO_2}) are typically recommended to characterise the V'_E–P_{ETCO_2} relationship. Each level is maintained for ~8–10 min, with the average V'_E and P_{ETCO_2} over the final 2–3 min providing the steady-state values. Consequently, the test is time-consuming, although transiently overshooting P_{ICO_2} beyond the required level can reduce the time required to attain the new V'_E steady state.

This concern is obviated, to a considerable extent, by the rebreathing method of Read *et al.* (1967), which takes a small fraction of the time to perform while providing effectively the same $\Delta V'_E/\Delta P_{ETCO_2}$ value as the steady-state method. The individual rebreathes from a 6–7-L bag initially containing ~7% carbon dioxide, balance oxygen. The high initial P_{ICO_2} is designed to raise P_{aCO_2} rapidly to, or close to, the mixed-venous level, such that the subsequent rebreathing provides an effectively linear increase in P_{ETCO_2}, P_{aCO_2} and P_{CO_2} at central chemoreceptor sites; the high inspired oxygen tension (P_{IO_2}) maintains P_{aO_2} above levels for which variations in carotid chemosensitivity would influence the V'_E–P_{ETCO_2} response slope.

The resulting V'_E–P_{ETCO_2} relationship is shifted to the right of the steady-state relationship, reflecting both the transit delay between the lungs and sites of chemoreception and the V'_E response kinetics to the hypercapnia. The rebreathing test is currently the more common means of assessing ventilatory carbon dioxide responsiveness, although it is important to recognise that the carbon dioxide responsiveness obtained by this hyperoxic method reflects only central chemoreflex activity.

The V'_E–P_{ETCO_2} relationship is not linear for all values of P_{ETCO_2}. That is, in contrast to the extrapolated dashed lines in figure 1, in the hypocapnic range (*e.g.* with acute hyperventilation or a sufficient degree of hypoxia) there is a region of virtual insensitivity to increasing P_{CO_2}. The transition from the insensitive to the sensitive region is considered to reflect a ventilatory recruitment threshold. The difference between this threshold P_{CO_2} and the low P_{ETCO_2} at which apnoea ensues is thought to be important in conditions such as sleep apnoea. Also, as this threshold is lower in hypoxia than in hyperoxia, it may be useful in better understanding how carotid body and central chemoreceptor afferent projections interact (*e.g.* additively or multiplicatively). As a practical expedient, the eucapnic difference in P_{ETCO_2} between hypoxic and hyperoxic conditions can be used as an index of the threshold change; Duffin (2011) has suggested P_{ETO_2} values of 150 and 50 mmHg for this assessment.

Estimation of ventilatory response to hypoxia

In humans the ventilatory response to hypoxia, if defined under isocapnic conditions, is considered solely to reflect carotid chemoreceptor activity, although recent animal studies have also suggested involvement of astrocytes located within brainstem respiratory integrating regions. The carotid body sensing mechanisms for hypoxia (through oxygen tension (P_{O_2})) and CO_2–H^+ status remain contentious, but a general postulate is that depolarising receptor potentials are generated in glomus or Type I cells *via* inhibition of oxygen- and pH-regulated potassium channels, leading to voltage-gated calcium ion entry, neurotransmitter release and excitation of carotid sinus nerve afferent projections to the brainstem. Both constant-concentration inspirate and rebreathing techniques have been successfully used for characterisation of the ventilatory response to hypoxia.

The pattern of the V'_E response to a step decrease of P_{ETO_2} is not monotonic, even with P_{ETCO_2} being maintained constant by controlling the inspired level (*i.e.* isocapnic hypoxia). There is an initial increase to a peak, usually well within 5 min, followed by a slow reduction (termed 'hypoxic ventilatory decline') to a final steady state (figure 2a). The initial increase is considered to be the carotid body component, while the subsequent decline is proposed to result from:

1) the hypoxia-mediated increase in cerebral blood flow, which reduces the degree of central chemoreceptor stimulation as a result of cerebral carbon dioxide washout; and

2) altered neurotransmission leading to depression of brainstem respiratory neurones.

If analysis of the hypoxic step V'_E response is limited to the initial (or primary) response phase, then the resulting V'_E–P_{aO_2} relationship over a range of increasingly hypoxic inspirates is curvilinear, with the V'_E rate of change approaching infinity at a P_{aO_2} of ~30 mmHg. Naturally, at higher isocapnic P_{CO_2} levels, the curvature constant of the response is increased as a result of greater hypoxic–hypercapnic interaction at the carotid bodies. It is recommended that the individual be switched to air or even a mildly hyperoxic mixture between successive hypoxic steady states to avoid the central complications of hypoxia. If, instead of isocapnia being maintained in this test, P_{aCO_2} is allowed to decrease spontaneously as V'_E increases (poikilocapnia), then both the peak initial V'_E response and the final level achieved after the hypoxic ventilatory decline are reduced.

A rebreathing test, notionally similar to the Read–Leigh test of carbon dioxide sensitivity, yields considerably greater data density in a significantly shorter period, although the requirement for isocapnia throughout the test does demand a degree of sophistication in avoiding the otherwise progressive hypercapnia by means of a carbon dioxide absorbing system. The resulting curvilinear response to the progressive isocapnic hypoxia is shown in figure 2b for two individuals differing markedly in hypoxic sensitivity. There is little, from a physiological standpoint, to choose between an exponential and a hyperbolic characterisation of the response. The conflicting issues

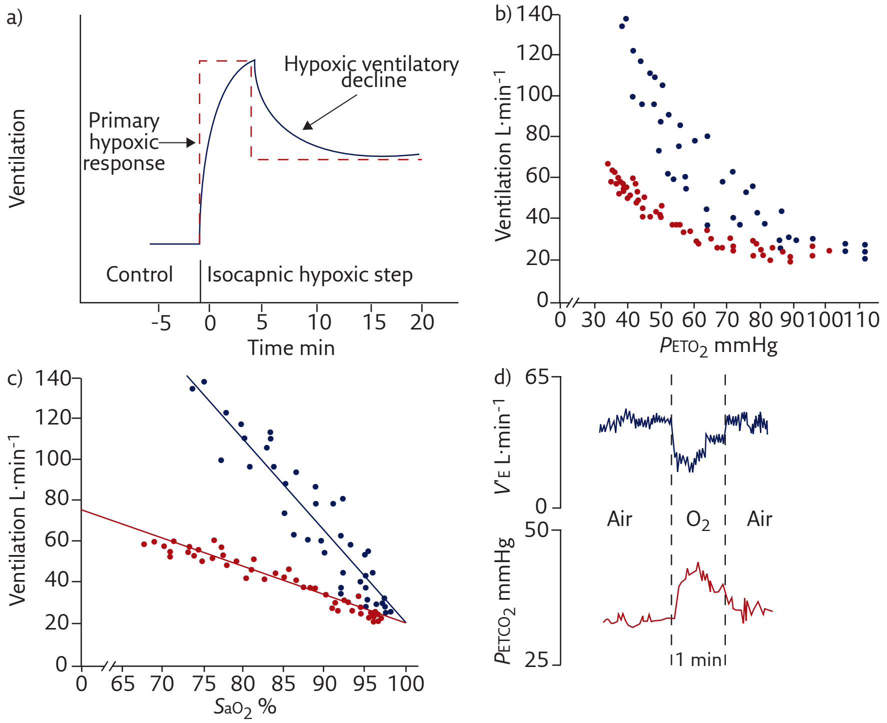


Figure 2. a) V'_{E} time-course to prolonged isocapnic step-decrease in P_{ETO_2}. b and c) Ventilatory response to progressive isocapnic hypoxia (in two individuals) as a function, respectively, of P_{ETO_2} and S_{aO_2}. d) Ventilatory time-course to a hyperoxic step-increase in an exercising hypoxic individual with alveolar proteinosis. b and c) Reproduced from Rebuck et al. (1981). d) Reproduced from Wasserman et al. (1981).

regarding the most appropriate index for hypoxic response characterisation appear to be obviated (on empirical grounds) by the demonstration that the curvilinear V'_{E}–P_{aO_2} relationship can be transformed into a linear relationship by substituting S_{aO_2} for P_{aO_2} (figure 2c):

$$V'_{\text{E}} = G \cdot S_{\text{aO}_2} + V'_{\text{E}}(0)$$

where $V'_{\text{E}}(0)$ is the baseline V'_{E} and the slope parameter G is the hypoxic responsiveness quantifier. G has been shown to average ~1.5±1.0 (average±SD) $\text{L}\cdot\text{min}^{-1}$ per % decrease of S_{aO_2} in normal individuals. At higher isocapnic levels, G is increased as a result of the potentiating effect of carbon dioxide on carotid body chemosensitivity, which sums with the further central CO_2–H^+ stimulation.

In addition to 1) the ease of measuring S_{aO_2} noninvasively by pulse oximetry (S_{pO_2}) and 2) averting any assumption regarding the difference between P_{ETO_2} and P_{aO_2}, the linearity of the V'_{E} response makes this rebreathing method a very practical means of assessing hypoxic ventilatory responsiveness. It is important to recognise, however, that the ventilatory stimulus is P_{aO_2}; S_{aO_2} is merely a practical expedient, with uncertainties regarding the influence of conditions altering haemoglobin affinity for oxygen.

The current degree of an individual's hypoxic ventilatory drive may also be estimated by the hypoxia-withdrawal test of Dejours (1962). If a particular level of P_{aO_2} is established by inhalation of a hypoxic gas mixture, or noting the spontaneous P_{aO_2} if the individual is already hypoxaemic (as in figure 2d for an exercising individual with alveolar proteinosis), then the abrupt administration of 100% oxygen will acutely suppress carotid body hypoxic responsiveness and cause V'_E to fall transiently and rapidly. The maximum decrease in V'_E as a fraction of the total hypoxic V'_E provides the index of hypoxic ventilatory drive. In addition to the assumption (probably justified in humans) that the consequently high P_{O_2} level actually silences the carotid body chemoreceptors, the validity of the Dejours test depends upon the V'_E decrement having reached its nadir prior to the subsequently increased P_{aCO_2} (caused by the reduced V'_E) influencing central sites of carbon dioxide chemosensitivity. As the nadir of the V'_E response commonly occurs ~20–25 s after the hypoxic–hyperoxic transition, there is some uncertainty regarding this latter point. Although this test is quite easy to perform and provides a useful qualitative estimate of hypoxic ventilatory responsiveness, it remains to be precisely standardised and quantified.

The peripheral-chemosensory potentiation of the ventilatory carbon dioxide response by hypoxia may also be used to provide an index of hypoxic ventilatory responsiveness: *i.e.* as the increase in V'_E between the hyperoxic (peripheral chemoreceptors silenced) and the hypoxic ($P_{aO_2}=40$ mmHg) V'_E-P_{aCO_2} relationships, measured at a standard P_{aCO_2} target level of 40 mmHg (ΔV_{40}).

Conclusion

Tests to discern abnormalities of carbon dioxide and hypoxic ventilatory responsiveness, while relatively straightforward to implement, can be challenging to interpret because of the complexity of the chemoreflexes. That is, they provide indices of the sensitivity of the entire reflex arc only. Judgements regarding particular foci of dysfunction may therefore require additional assessments whose description is beyond the scope of this brief section. These tests are expressly designed to reflect 'open-loop' control-system behaviour, allowing ventilatory responsiveness to be evaluated in isolation without the further complexity of considering how the V'_E responses feed-back on P_{aCO_2} and P_{aO_2} a through the physiological 'plant' of body gas stores and pulmonary gas exchange. Finally, it should also be noted that currently available tests, being acute in character, may provide a less comprehensive view of ventilatory function in more chronic blood–gas and acid–base impairments.

Further reading

- Buckler KJ (2015). TASK channels in arterial chemoreceptors and their role in oxygen and acid sensing. *Pflugers Arch*; 467: 1013–1025.
- Cunningham DJC, *et al*. Integration of respiratory responses to changes in alveolar partial pressures of CO_2 and O_2 and in arterial pH. *In*: Widdicombe JG, *et al.*, eds. Handbook of Physiology, Respiration. Vol II, Control of Breathing, Part 2. Washington DC, American Physiological Society, 1986; pp. 475–528.
- Dejours P (1962). Chemoreflexes in breathing. *Physiol Rev*; 42: 335–358.
- Dempsey JA, *et al*. (2004). The ventilatory responsiveness to CO_2 below eupnoea as a determinant of ventilatory stability in sleep. *J Physiol*; 560: 1–11.
- Duffin J (2011). Measuring the respiratory chemoreflexes in humans. *Respir Physiol Neurobiol*; 177: 71–79.
- Edelman NH, *et al*. (1997). Effects of CNS hypoxia on breathing. *In*: Crystal RG, *et al*., eds. The Lung: Scientific Foundations. 2nd Edn. New York, Raven Press; pp. 1757–1765.

- Gourine AV, *et al.* (2017). On the existence of a central respiratory oxygen sensor. *J Appl Physiol*; 123: 1344–1349.
- Guyenet PG, *et al.* (2016). Proton detection and breathing regulation by the retrotrapezoid nucleus. *J Physiol*; 594: 1529–1551.
- Kumar P, *et al.* (2012). Peripheral chemoreceptors: function and plasticity of the carotid body. *Compr Physiol*; 2: 141–219.
- López-Barneo J (2018). Oxygen sensing and stem cell activation in the hypoxic carotid body. *Cell Tissue Res*; 372: 417–425.
- Nattie E, *et al.* (2012). Central chemoreceptors: locations and functions. *Compr Physiol*; 2: 221–254.
- Pamenter ME, *et al.* (2016). Time domains of the hypoxic ventilatory response and their molecular basis. *Compr Physiol*; 6: 1345–1385.
- Read DJC, *et al*. (1967). Blood–brain tissue $P\mathrm{CO}_2$ relationships and ventilation during rebreathing. *J Appl Physiol*; 23: 53–70.
- Rebuck AS, *et al*. (1981). Measurement of ventilatory responses to hypercapnia and hypoxia. *In*: Hornbein T, ed. The Regulation of Breathing. New York, Dekker; pp. 745–772.
- Sepúlveda FV, *et al.* (2015). Molecular aspects of structure, gating, and physiology of pH-sensitive background $\mathrm{K}_{2\mathrm{P}}$ and Kir K+-transport channels. *Physiol Rev*; 95: 179–217.
- Severinghaus JW (1976). Proposed standard determination of ventilatory responses to hypoxia and hypercapnia in man. *Chest*; 70: Suppl, 129–131.
- Teppema LJ, *et al.* (2010). The ventilatory response to hypoxia in mammals: mechanisms, measurement, and analysis. *Physiol Rev*; 90: 675–754.
- Ward SA (1994). Assessment of peripheral chemoreflex contributions to ventilation during exercise. *Med Sci Sports Ex*; 26: 303–310.
- Wasserman K, *et al*. (1981). Respiratory control during exercise. *In*: Widdicombe JG, ed. International Review of Physiology, Respiratory Physiology III. Baltimore, Univ Park Press; pp. 149–211.
- Zhang S, *et al.* (2000). Methodological and physiological variability within the ventilatory response to hypoxia in humans. *J Appl Physiol*; 88: 1924–1932.

Respiratory mechanics

Daniel Navajas and Ramon Farré

Pulmonary ventilation is determined by the resistive and elastic properties of the lungs and chest wall, and by the driving pressure of the respiratory muscles. Both the lungs and chest wall are elastic structures. The lungs have a very small resting volume. Above this volume, the lungs are distended, exerting an inward elastic recoil pressure (P_{L}) that rises markedly with lung volume (V_{L}). The chest wall has a much higher resting volume, exhibiting outward and inward elastic recoil pressure (P_{CW}) below and above its resting volume, respectively.

At end-expiratory volume during quiet breathing (functional residual capacity (FRC)) in a healthy subject, the respiratory muscles are relaxed and the lungs and chest wall reach the combined resting state (figure 1). In this situation, the inward P_{L} is counterbalanced by the outward P_{CW} and the alveolar pressure (P_{alv}) equals atmospheric pressure. Inspiration is produced by activation of inspiratory muscles. The outward muscular pressure (P_{mus}) expands the chest wall, thereby lowering pleural pressure (P_{pl}). This drop in P_{pl} expands the lung and decreases P_{alv} to sub-atmospheric values. The mouth–alveolar pressure gradient drives inspiratory flow. During quiet breathing in a normal subject, expiration is achieved by relaxing the inspiratory muscles. The net inward elastic recoil of the total respiratory system (P_{rs}), the sum of P_{L} and P_{CW}, tends to return the system to the overall equilibrium volume, increasing P_{alv} to above mouth pressure (P_{mo}) and driving expiratory flow. The activation of the expiratory muscles results in a faster expiration.

Airway resistance

The airflow generated by the pressure gradient between the mouth and the alveoli is determined by airway resistance (R_{aw}), defined as:

$$R_{\mathrm{aw}} = \frac{P_{\mathrm{mo}} - P_{\mathrm{alv}}}{V'}$$

Key points

- P_{alv} is lower and higher than P_{ao} during inspiration and expiration, respectively.
- The lungs exert inward elastic recoil that increases with V_{L}.
- Body plethysmography allows for the measurement of both R_{aw} and V_{L}.
- The FOT allows the measurement of respiratory resistance during spontaneous breathing with minimum patient collaboration.
- Respiratory mechanics can be monitored in sedated mechanically ventilated patients performing post-inspiratory and post-expiratory pauses.

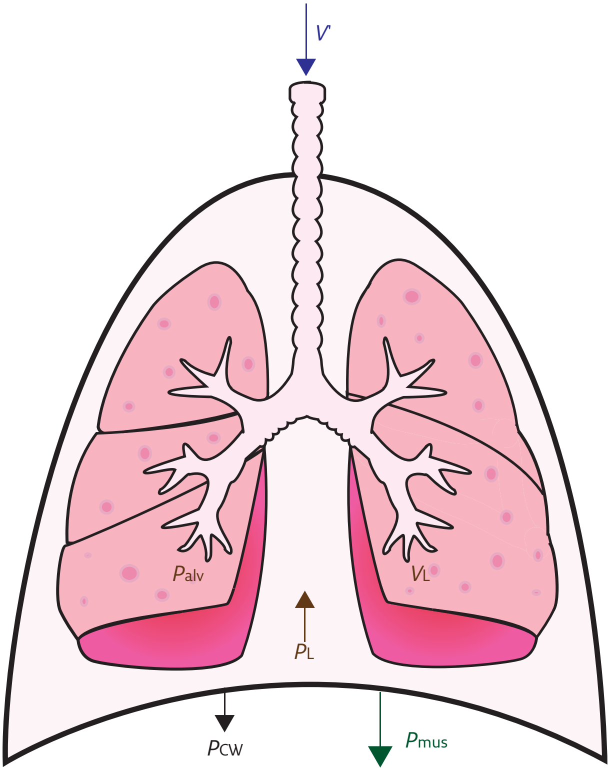


Figure 1. *Mechanical behaviour of the respiratory system.*

where V' is the gas flow. In healthy adults, R_{aw} measured at FRC is ~2 $hPa \cdot s \cdot L^{-1}$. Intrathoracic airway calibre increases as lungs expand, resulting in a hyperbolic dependence of R_{aw} on lung volume. Therefore, an approximately linear relationship is obtained by computing airway conductance (G_{aw}):

$$G_{aw} = \frac{1}{R_{aw}}$$

Since large lungs have wider airways, the specific airway resistance (sR_{aw}) computed as:

$$sR_{aw} = R_{aw} \cdot \mathrm{FRC}$$

provides a resistance measurement normalised for differences in lung size. Similarly, specific airway conductance (sG_{aw}) is defined as:

$$sG_{aw} = \frac{G_{aw}}{\mathrm{FRC}}$$

Body plethysmography

Measurement of R_{aw} requires the recording of airflow and driving pressure. Airflow can be recorded with a pneumotachograph connected to the mouth. P_{mo} is simply atmospheric pressure or, alternatively, it can be readily measured with a pressure transducer. As the alveolar airspace is not directly accessible, P_{alv} can be estimated by means of a whole-body plethysmograph (figure 2). This technique involves the

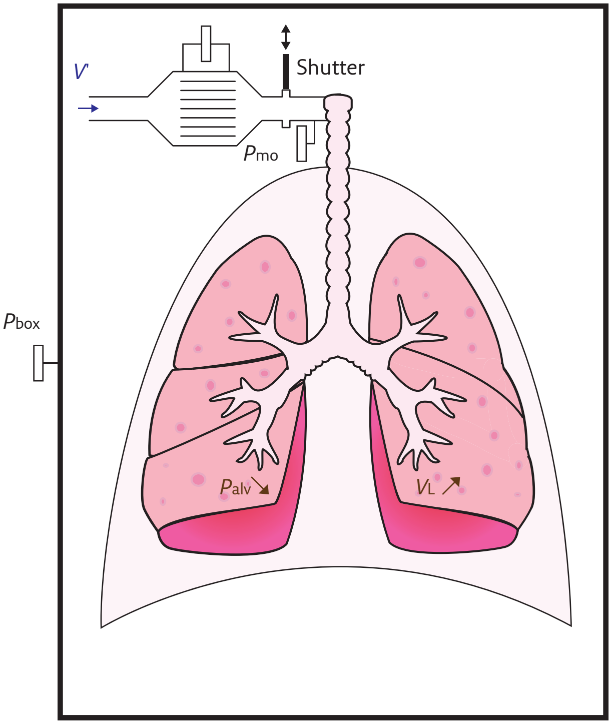


Figure 2. Measurement of R_{aw} *by body plethysmography.*

subject sitting inside a closed cabin breathing the gas from the box. The mouth can be occluded with a shutter coupled to the mouthpiece. First, the shutter is opened and the ratio between V' and the pressure within the box (P_{box}) is measured during breathing (V'/P_{box}).

During inspiration, air moves from the box to the lung. The inspired gas takes on a higher volume in the lungs than in the box due to the decrease in pressure ($P_{\mathrm{alv}}<P_{\mathrm{box}}$), the increase in temperature (37°C) and the addition of water vapour. The calibration ratio of the plethysmograph (k) is experimentally determined by closing the shutter at FRC and recording P_{mo} and P_{box} during gentle respiratory efforts against the occlusion. Under zero airflow conditions, $P_{\mathrm{alv}} \approx P_{\mathrm{mo}}$ and

$$k = \frac{P_{\mathrm{alv}}}{P_{\mathrm{box}}}$$

Therefore,

$$R_{\mathrm{aw}} = \frac{P_{\mathrm{alv}}}{V'} = \frac{k \cdot P_{\mathrm{box}}}{V'}$$

Body plethysmography measurements of R_{aw} are usually computed at low respiratory flows (<0.5 L) recorded during shallow panting to minimise the effects of temperature changes during inspiration and expiration. Alternatively, measurements can be made during quiet breathing after computer correction for changes in the physical conditions of the gas.

Whole-body plethysmography is the procedure most commonly used to measure R_{aw}. An added advantage of this technique is that it provides an FRC measurement for the computation of sR_{aw}. However, the device is bulky and expensive, and is not suited to measurement in supine patients.

Forced oscillation technique

In addition to R_{aw}, lung and chest wall tissues also exhibit resistive load because of internal frictional resistance to motion. Resistance of the total respiratory system (R_{rs}) is the sum of R_{aw} and tissue resistance. The tissue component of R_{rs} is generally small in comparison with R_{aw}.

R_{rs} can be measured during quiet breathing by the forced oscillation technique (FOT). This technique is based on applying a small-amplitude (±1 hPa) pressure oscillation to the patient's mouth or nose with a loudspeaker or a small pump. R_{rs} is computed as the ratio of forced pressure oscillation and in-phase flow. The ratio between forced pressure and the out-of-phase flow defines the reactance that provides a combined measurement of the inertial and elastic properties of the respiratory system. Forced oscillation is applied at frequencies (>4 Hz) higher than the breathing rate to facilitate the separation of forced oscillation from tidal breathing. The use of multifrequency oscillation (usually 4–32 Hz) provides a measurement of the frequency dependence of respiratory mechanics.

Current FOT devices are portable and easy to use. The technique does not require any special collaboration from the patient and measurements can be performed supine. Changes in R_{rs} during the breathing cycle can be precisely monitored. Moreover, FOT can be coupled to mechanical ventilators. Therefore, FOT is especially useful for epidemiological studies, measurements in infants, and monitoring respiratory mechanics in patients during sleep and mechanical ventilation.

Lung compliance

The elastic behaviour of the lung is described by the P_{L}–V_{L} relationship. Lung deformability is measured as lung compliance (C_{L}), defined as the change in volume divided by the change in pressure:

$$C_{\mathrm{L}} = \frac{\Delta V_{\mathrm{L}}}{\Delta P_{\mathrm{L}}}$$

ΔV_{L} can readily be measured with a spirometer connected to the mouth. The measurement of ΔP_{L} requires the simultaneous recording of P_{pl} and P_{alv}. P_{pl} is usually estimated from the oesophageal pressure (P_{oes}) recorded with a small balloon attached to the tip of a catheter introduced through the nose into the lower oesophagus. P_{alv} is estimated in the mouth during brief flow interruptions. In practice, the subject performs a full inspiration followed by a very slow expiration to FRC. A shutter attached to the spirometer performs successive brief (~1 s) occlusions during expiration. The P_{L}–V_{L} relationship is curvilinear, with C_{L} decreasing markedly with volume. C_{L} is habitually computed in the range of tidal volume at rest (between FRC and FRC +0.5 L). In the normal adult, C_{L} is ~0.2 $\mathrm{L \cdot hPa^{-1}}$. The elastic behaviour of the lung can also be characterised by lung elastance (E_{L}), defined as the reciprocal of C_{L}:

$$E_{\mathrm{L}} = \frac{1}{C_{\mathrm{L}}}$$

Chest wall compliance (C_{CW}) is computed as:

$$C_{\mathrm{CW}}=\frac{\Lambda V_{\mathrm{L}}}{\Delta P_{\mathrm{CW}}}$$

In healthy subjects, the value of C_{CW} is comparable to that of C_{L}. Since the elastic pressure of the respiratory system is $P_{\mathrm{rs}}=P_{\mathrm{L}}+P_{\mathrm{CW}}$, the compliance of the respiratory system (C_{rs}) is related to C_{L} and C_{CW} as:

$$\frac{1}{C_{\mathrm{rs}}}=\frac{1}{C_{\mathrm{L}}}+\frac{1}{C_{\mathrm{CW}}}$$

C_{rs} and C_{CW} can only be measured during complete respiratory muscle relaxation, which is extremely difficult to achieve in conscious patients.

Measurement of respiratory mechanics in mechanical ventilation

Respiratory mechanics can be measured in sedated mechanically ventilated patients by recording airflow and pressure at the airway opening (P_{ao}). The driving pressure required to overcome the elastic and resistive loads (E_{rs} and R_{rs}, respectively) of the respiratory system is:

$$P_{\mathrm{ao}}=R_{\mathrm{rs}}\cdot V'+E_{\mathrm{rs}}\cdot V$$

where V is volume. R_{rs} and E_{rs} can be computed by least-squares fitting of this equation to P_{ao}, V' and V recordings.

In patients ventilated with a constant flow waveform, R_{rs} and E_{rs} can also be measured by performing a post-inspiratory pause. Flow interruption results in a sharp drop in pressure from the peak value at end inspiration (P_{max}) to P_1, followed by a slow decay to a plateau (P_2). The sudden decrease in P_{ao} is associated with the resistive load of the airways. Therefore, R_{aw} is estimated as:

$$R_{\mathrm{aw}}=\frac{P_{\mathrm{max}}-P_1}{V'}$$

A higher value of resistance due to the contribution of tissue viscoelasticity and gas redistribution within the lungs is computed from the pressure drop to the plateau ($P_{\mathrm{max}}-P_2$).

The additional performance of a post-expiratory pause allows E_{rs} to be computed as the ratio of pressure and volume changes at the end of the post-inspiratory and post-expiratory pauses.

Further reading

- Bates JH, *et al.* (2011). Oscillation mechanics of the respiratory system. *Compr Physiol*; 1: 1233–1272.
- Beydon N, *et al.* (2007). An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med*; 175: 1304–1345.
- Farre R, *et al.* (2004). Noninvasive monitoring of respiratory mechanics during sleep. *Eur Respir J*; 24: 1052–1060.

- Galetke W, *et al.* (2007). Reference values for dynamic and static pulmonary compliance in men. *Respir Med*; 101: 1783–1789.
- Gibson GJ (2009). Respiratory mechanics. *In:* Gibson GJ, ed. Clinical Tests of Respiratory Function. 3rd Edn. London, Hodder Arnold; pp. 3–52.
- Grinnan DC (2005). Clinical review: respiratory mechanics in spontaneous and assisted ventilation. *Crit Care*; 9: 472–484.
- Hyatt RE, *et al.* (2008). Other tests of lung mechanics: resistance and compliance. *In:* Hyatt RE, *et al.*, eds. Interpretation of Pulmonary Function Tests. A Practical Guide. 3rd Edn. Philadelphia, Lippincott Williams & Wilkins; pp. 75–86.
- Lucangelo U, *et al.* (2007). Lung mechanics at the bedside: make it simple. *Curr Opin Crit Care*; 13: 64–72.
- Oostveen E, *et al.* (2003). The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J*; 22: 1026–1041.
- Pride NB (1999). Airflow resistance. *In:* Hughes JMB, *et al.*, eds. Lung Function Tests: Physiological Principles and Clinical Applications. London, W.B. Saunders; pp. 27–44.

Gas transfer

J. Mike Hughes

Transfer factor of the lung for carbon monoxide

Apart from spirometry, the transfer factor of the lung for carbon monoxide (T_{LCO}) is the most frequently performed pulmonary function test. It focuses on the integrity of the alveolar (gas exchanging) part of the lung. T_{LCO} can detect abnormalities limited to the pulmonary microcirculation, the only routine test that can do so. It helps to think of T_{LCO} as a measure of the anatomy of the alveolar region, whereas blood gas measurements (P_{aO_2} and P_{aCO_2}) measure a physiological efficiency, which involves airways and larger blood vessels, as well as alveolar structures. For example, T_{LCO} is normal in asthma (alveoli are uninvolved), but the P_{aO_2} may be considerably reduced.

Definition

The transfer factor (called D_{LCO} in North America) measures the surface area available for gas exchange. It is closely related to the oxygen diffusing capacity. T_{LCO} is the quantity of inhaled carbon monoxide absorbed, per unit time and per unit carbon monoxide partial pressure. The pressure gradient is the alveolar–plasma carbon monoxide tension (P_{CO}) difference. Carbon monoxide is chosen for alveolar–capillary exchange because, after diffusing into capillary blood, carbon monoxide binds to Hb as carboxy-Hb (HbCO), but at an extremely low partial pressure (P_{CO}). Plasma P_{CO} is so low that it is not usually measured, but it may reach significant levels in current smokers. Carbon monoxide uptake is independent of blood flow, but it is dependent on the number of Hb-binding sites, *i.e.* on capillary volume, as well as molecular diffusion across the alveolar–capillary membranes. 'Transfer' is the better term, because chemical reaction as well as 'diffusion' is involved.

Technique

Nearly all clinical laboratories use the single-breath technique of Ogilvie *et al*. (1957). The T_{LCO} is measured during a 10-s breath-hold at maximal inspiration (this volume is equivalent to the TLC).

Key points

- T_{LCO} measures alveolar function.
- T_{LCO} is the product of K_{CO} and V_A.
- K_{CO} (or T_L/V_A) is the more specific index of alveolar integrity.
- K_{CO} is low in emphysema and fibrosis.
- K_{CO} is high in extrapulmonary restriction.

Breath-holding at TLC optimises the distribution of the inhaled marker gases (helium (or another insoluble gas such as methane) and carbon monoxide), and makes T_{LCO} independent of ventilation distribution. In the breathing manoeuvre the subject is asked to:

- exhale slowly to residual volume;
- make a signal;
- inspire rapidly to full inflation; and
- hold their breath until instructed to breathe out (after about 10 s).

After the voluntary breath-hold, exhalation occurs rapidly (there is no need for a forced expiration) and a 0.5–1.0 L 'alveolar sample' is collected, once the first 500 mL of 'anatomic dead space contaminated' gas has been expired, from which water vapour and carbon dioxide are absorbed before helium (or a substitute) and carbon monoxide concentrations are analysed. The 500 mL dead space 'discard volume' may be reduced if anatomic dead space is measured directly using the Fowler technique with expired gas continuously monitored with rapid gas analysers (RGAs) (see Graham *et al.* (2017), p. 9). In other words, with a sampling line in the breathing tube on the mouthward side of the reservoir bag (c in figure 1), inspired and expired concentrations of carbon monoxide (and nitric oxide) and an insoluble marker gas (helium, methane, neon) would be monitored continuously. The effective breath-hold time is calculated according to Jones *et al.* (1961).

Calculation of the T_{LCO}

The key point is that the T_{LCO} is the product of two measurements, 1) the alveolar volume (V_{A}) and 2) the rate of alveolar uptake of carbon monoxide, given by the

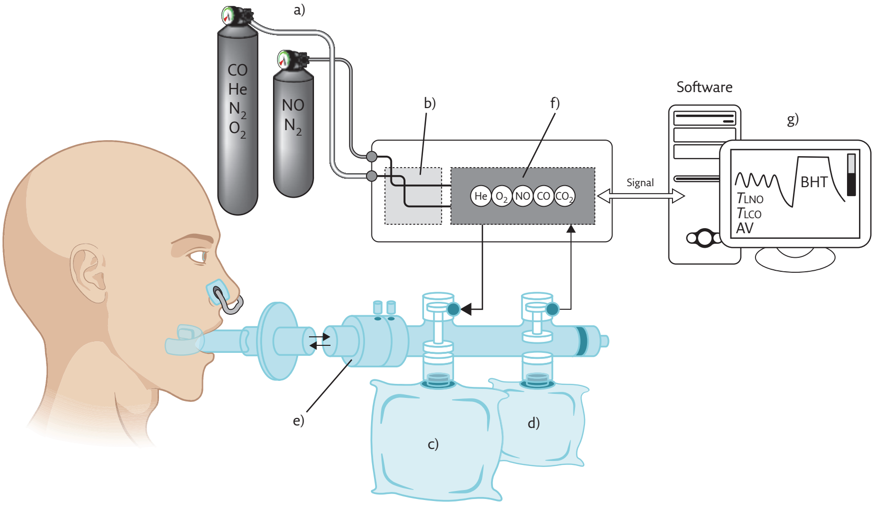


Figure 1. Single breath T_{LCO} *set-up: a) gas sources; b) regulators; c) reservoir for inspiratory mixture; d) sampling bag; e) flowmeter, with disposable bacterial and viral filter screen between it and the subject; f) gas analysers; and g) software with breathing protocol shown on the computer screen. Breath hold time is set automatically, calculated from 0.33× inspired time to expired mid-collection time. AV: alveolar volume; BHT: breath holding time. Figure partially created using BioRender. Reproduced from Giraud* et al. *(2017) with permission from the publisher.*

slope (k_{CO}) of alveolar uptake of CO (figure 2), which is equivalent to the transfer coefficient of the lung for carbon monoxide (K_{CO}). During the breath-hold at maximal inspiration, V_{A} should equal TLC minus the anatomical dead space (97–98% of the TLC). In practice, V_{A} in normal subjects is 93.5±6.6% (6.6%=1SD) of multi-breath calculations of TLC (Roberts *et al.*, 1990). The 10-s breath-hold is insufficient time for complete gas mixing; in airflow obstruction, the measured V_{A} may be much less than 80% of the actual TLC (measured by multi-breath gas dilution or plethysmography).

The k_{CO} is the rate of alveolar uptake of carbon monoxide during the breath-hold (the slope in figure 2). It is a rate constant with units of s^{-1} or min^{-1}. When normalised to barometric pressure (minus water vapour pressure) ($P\mathrm{b}^*$), $k_{\mathrm{CO}}/\mathrm{Pb}^* = k^{\dagger}_{\mathrm{CO}}$ ($\mathrm{min}^{-1}\cdot\mathrm{kPa}^{-1}$). The final step in the calculation of T_{LCO} is the multiplication of $k^{\dagger}_{\mathrm{CO}}$ by V_{A} (in mmol: 1mmol=22.4 mL standard temperature, pressure and dry).

$$k^{\dagger}_{\mathrm{CO}} \times V_{\mathrm{A}} = T_{\mathrm{LCO}}\ (\mathrm{mmol}\cdot\mathrm{min}^{-1}\cdot\mathrm{kPa}^{-1})$$

The next step is the division of T_{LCO} by V_{A} in L (body temperature, pressure, saturated at 37ºC, not mmol):

$$T_{\mathrm{LCO}}/V_{\mathrm{A}} = K_{\mathrm{CO}}\ (\mathrm{mmol}\cdot\mathrm{min}^{-1}\cdot\mathrm{kPa}^{-1}\cdot\mathrm{L}^{-1})$$

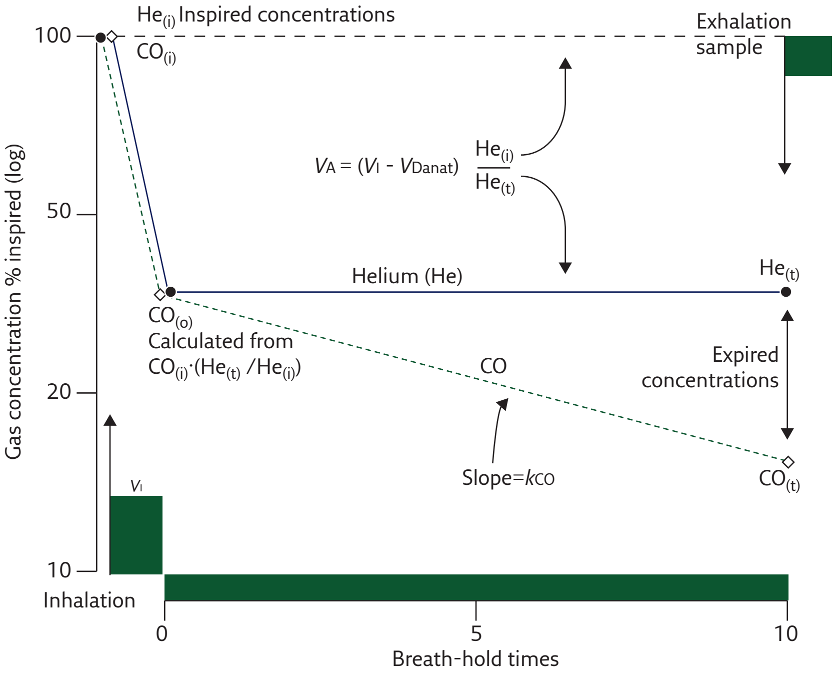


Figure 2. T_{LCO}*: carbon monoxide and helium analysis. Carbon monoxide and helium concentrations versus breath-hold time to illustrate the origin and calculation of the two components (slope of the transfer coefficient of the lung for CO (*k_{CO}*) and alveolar volume (*V_{A}*)) from which* T_{LCO} *is derived.* $\mathrm{CO}_{(i)}$ *and* $\mathrm{CO}_{(t)}$ *are carbon monoxide concentrations inspired (i) and after exhalation (with dead space discard) at time t after breath-hold (the same for* $\mathrm{He}_{(i)}$ *and* $\mathrm{He}_{(t)}$*).* $\mathrm{CO}_{(0)}$ *is the calculated alveolar concentration at breath-hold start before alveolar uptake has begun.* V_{I}*: inspired volume.* V_{Danat}*: anatomic dead space.*

Table 1. Physiological influences on the T_{LCO} *and the* K_{CO}

	T_{LCO}	K_{CO}
Anaemia	↓	↓
Cardiac output increase	↑	↑
$P_{\mathrm{AO_2}}$ increase	↓	↓
V_{A} ↓ (reduced alveolar expansion)	↓	↑↑
V_{A} ↓ (reduction in number of aerated alveoli)	↓	↑

but the units only differ from $k^{\dagger}_{\mathrm{CO}}$ by a constant factor except for small variations in Pb* ($K_{\mathrm{CO}}/k^{\dagger}_{\mathrm{CO}}$ ~37). Thus, $T_{\mathrm{LCO}}/V_{\mathrm{A}}$ ($=K_{\mathrm{CO}}$) remains, in essence, the rate constant for alveolar carbon monoxide uptake. This terminology is confusing (Hughes *et al.*, 2012) because the impression is given that $T_{\mathrm{LCO}}/V_{\mathrm{A}}$ ($=K_{\mathrm{CO}}$) 'corrects' the T_{LCO} for variations in V_{A}. Unfortunately, this is not the case, and with normal lung structure K_{CO} at 50%, predicted TLC (as % of K_{CO} at predicted TLC) is 150% not the 100% required by an accurate volume 'correction'.

If V_{A} remains constant, T_{LCO} and K_{CO} will change equally (as % predicted). There are formulae to correct T_{LCO} for anaemia, so the Hb level should always be known. Smoking raises plasma P_{CO} (a 'back pressure' effect) and produces HbCO, displacing $\mathrm{HbO_2}$ (an 'anaemia' effect), so smoking should be prohibited for 12–24 h before testing. Oxygen breathing with an increase in alveolar oxygen tension ($P_{\mathrm{AO_2}}$) reduces T_{LCO} and K_{CO} by competitive antagonism between oxygen and carbon monoxide; it is the basis of the Roughton–Forster equation which partitions $1/T_{\mathrm{LCO}}$ (transfer resistance) into the sum of $1/D_{\mathrm{M}}$ (alveolar–capillary membrane diffusion resistance) and $1/\theta V_{\mathrm{c}}$ (transfer resistance of red cells).

When V_{A} is reduced and lung structure (or the remaining lung structure) is normal, T_{LCO} and K_{CO} change in opposite directions (table1) if the cause is:

- reduced alveolar expansion, *e.g.* extrapulmonary restriction, or
- a reduction in aerated alveolar units, *e.g.* pneumonectomy or consolidation or atelectasis of lobes or lobules.

Other causes of a reduced V_{A} are: 1) diffuse alveolar damage (emphysema or fibrosis) (T_{LCO} and K_{CO} both reduced); and 2) airflow obstruction (V_{A} is low due to poor gas mixing), where T_{LCO} and K_{CO} are variable, both being low in emphysema and normal or high in asthma.

Implications of $K_{\mathrm{CO}} \times V_{\mathrm{A}} = T_{\mathrm{LCO}}$

Transfer coefficient of the lung $T_{\mathrm{L}}/V_{\mathrm{A}}$ does not correct T_{LCO} for a low V_{A} because $T_{\mathrm{L}}/V_{\mathrm{A}}$ often rises when $T_{\mathrm{L}}/V_{\mathrm{A}}$ falls. $T_{\mathrm{L}}/V_{\mathrm{A}}$ is equivalent to K_{CO}, the rate constant for alveolar uptake of CO.

The same T_{LCO} (say 60% predicted) can arise from different combinations of K_{CO} and $T_{\mathrm{L}}/V_{\mathrm{A}}$, such as: 1) high K_{CO} and low V_{A} (extrapulmonary restriction); 2) low K_{CO} and normal $T_{\mathrm{L}}/V_{\mathrm{A}}$ (pulmonary vasculopathy); or 3) low-ish K_{CO} and low-ish $T_{\mathrm{L}}/V_{\mathrm{A}}$ (fibrosis) (table 2).

Transfer factor of the lung for nitric oxide

The transfer factor of the lung for nitric oxide (T_{LNO}) was introduced into clinical medicine by Guenard *et al.* (1987) and Borland *et al.* (1989). The methodology

Table 2. Different combinations of KCO *and* TL/VA *but a similar* TLCO

Diagnosis	*T*LCO % pred	*K*CO % pred	*V*A % pred	Comment
Inspiratory muscle weakness	59	120	50	Lack of alveolar expansion
Pneumonectomy	58	111	51	Localised loss of lung units
Diffuse interstitial lung disease	54	84	66	Alveolar capillary damage (loss of units)
Emphysema	54	59	91	Alveolar capillary damage (FEV1/FVC ratio reduced)
Idiopathic pulmonary hypertension	56	58	96	Microvascular damage (FEV1/FVC ratio normal)

Reproduced and modified from Hughes *et al.* (2012).

and calculations are the same as the *T*LCO, and both tests can be performed simultaneously in one single-breath manoeuvre. The rate of alveolar uptake of nitric oxide (*K*NO) is four to five times faster than *K*CO, so the breath-hold time is usually reduced to 5–6 s unless a very sensitive nitric oxide analyser is used. The faster uptake of nitric oxide is due to a two-fold (*versus* carbon monoxide) increase in diffusivity through the alveolar–capillary membranes, and a faster reaction with red blood cell Hb than carbon monoxide. The *T*LNO/*T*LCO and *K*NO/*K*CO ratios (they are identical since *V*A is common to both measurements) are 4.3–4.9 in normal subjects. The *T*LNO is less sensitive to physiological changes in the pulmonary circulation than the *T*LCO; the *T*LNO is independent of changes in haematocrit and P_{AO_2}. The *T*LNO/*T*LCO ratio is raised in pulmonary vascular disease and reduced in interstitial lung disease with fibrosis (*T*LNO and *T*LCO being themselves reduced in both circumstances). Further research is needed to assess role of the *T*LNO/*T*LCO ratio in pulmonary function testing and whether *T*LNO will supplant the *T*LCO. A recent issue of Respiratory Physiology and Neurobiology is entirely devoted to *T*LNO (see Zavorsky, 2017).

*T*LCO and *T*LNO: reference values, standardisation, and guidelines

The European respiratory Society (ERS), the American Thoracic Society (ATS) and the Global Lung Initiative (GLI) Network and their task forces have contributed much towards reference values and standardisation; the paper by Stanojevic *et al.* (2017) is the current gold standard for *T*LCO reference values (although work remains to be done on ethnic differences). Graham *et al.* (2017) have up-dated the technical specifications for the single breath *T*LCO, emphasising RGAs for carbon monoxide and the inert tracer gas; all future *T*LCO systems are likely to be fitted with RGAs, replacing the 500 mL sampling bag.

For *T*LNO, which is a more recent test, Zavorsky *et al.* (2017a,b) have published a standardisation document with details of the theory, technique of measurement and clinical applications; reference values for *T*LNO and *T*LCO, in a combined measurement, have been calculated by two groups (Zavorsky *et al*., 2017b and Munkholm *et al*., 2018). Reference values for the combined *T*LNO and *T*LCO in children have also appeared (Thomas *et al*, 2014).

Further reading

- Borland CD, *et al.* (1989). A simultaneous single breath measurement of pulmonary diffusing capacity with nitric oxide and carbon monoxide. *Eur Respir J*; 2: 56–63.
- Cooper BG, *et al.* (2017). The Global Lung Initiative (GLI) Network: bringing the world's respiratory reference values together. *Breathe (Sheff)*; 13 (3): e56–e64.
- Giraud X, *et al.* (2017). The measurement of *D*LNO and *D*LCO: a manufacturer's perspective. *Respir Physiol Neurobiol*; 241: 36–44.
- Graham BL, *et al.* (2017). Executive Summary: 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J*; 49: 16E0016.
- Guenard H, *et al.* (1987). Determination of lung capillary blood volume and membrane diffusing capacity in man by the measurementsof NO and CO transfer. *Respir Physiol*; 70: 113–120.
- Hughes JMB, *et al.* (2012). Examination of the carbon monoxide diffusing capacity *D*L,CO in relation to its *K*CO and *V*A components. *Am J Respir Crit Care Med*; 186: 132–139.
- Hughes JMB, *et al.* (2017). The *D*LNO/*D*LCO ratio: physiological significance and clinical implications. *Respir Physiol Neurobiol*; 241: 17–22.
- Jones RS, *et al.* (1961). A theoretical and experimental analysis of anomalies in the estimation of pulmonary diffusing capacity by the single breath method. *Q J Exp Physiol Cogn Med Sci*; 46: 131–143.
- Munkholm M, *et al.* (2018). Reference equations for pulmonary diffusing capacity of CO and NO in adult Caucasians. *Eur Respir J*; 52:1500677.
- Ogilvie CM, *et al.* (1957). A standardized breath holding technique for the clinical measurement of the diffusing capacity of the lung for carbon monoxide. *J Clin Invest*; 36: 1–17.
- Roberts CM, *et al.* (1990). Multi-breath and helium single breath dilution lung volumes as a test of airway obstruction. *Eur Respir J*; 3: 515–520.
- Stanojevic S, *et al.* (2017). Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J*; 50: 1700010.
- Thomas A, *et al.* (2014). The single-breath diffusing capacity of CO and NO in healthy children of European descent. *PLoS One*; 9: e113177.
- Zavorsky GS. (2017). Nitric oxide uptake in the lung: it is about time clinicians use this test routinely. *Respir Physiol Neurobiol*; 241: 1–2.
- Zavorsky GS, *et al.* (2017a). Can the measurement of pulmonary diffusing capacity for nitric oxide replace the measurement of pulmonary diffusing capacity for carbon monoxide? *Respir Physiol Neurobiol*; 241: 9–16.
- Zavorsky GS, *et al.* (2017b). Standardisation and application of the single-breath determination of nitric oxide uptake in the lung. *Eur Respir J*; 49: 1600962.

Arterial blood gas assessment

Paolo Palange and Alessandro Ferrazza

The fundamental function of the lung is to contribute to the homeostasis of the system by ensuring that pulmonary uptake of oxygen (V'_{O_2}) and clearance of carbon dioxide (V'_{CO_2}) match with whole-body bioenergetic requirements. We must look at pulmonary function as the first step of the O_2 transport chain from the atmosphere to mitochondria and the lung as a fundamental organ in CO_2, and thus pH, homeostasis.

Arterial blood gas analysis (ABG) provides direct measurements of P_{aO_2}, P_{aCO_2} and pH in arterial blood. In clinical practice, ABG is needed to assess both the severity and causes of pulmonary gas exchange impairment and acid–base (A–B) disequilibrium. ABG is one of the most useful diagnostic tests, not only in the critical care setting but also in general clinical practice, to assess patients with respiratory diseases and those with other disorders with potential impact pulmonary gas exchange and A–B disturbances (diabetes, heart failure and renal failure). Moreover, ABG is mandatory to establish the diagnosis of respiratory failure.

Modern equipment to perform ABG assessment uses electrodes to measure P_{aO_2}, P_{aCO_2} and pH. Other variables, such as bicarbonates (actual HCO_3^- and standard HCO_3^-), base excess (BE) and S_{aO_2}, are computed using well-defined equations.

A simple and practical two-step approach for ABG interpretation in the clinical setting is illustrated in figure 1. The first step aims to analyse pulmonary gas exchange status based primarily on P_{aO_2} and P_{aCO_2}, while the second step addresses the assessment of A–B status using P_{aCO_2}, pH and eventually, HCO_3^- (or BE). If serum electrolytes,

Key points

- Arterial blood gas analysis (ABG) is mandatory for the diagnosis of respiratory failure and of acid–base (A–B) disorders.
- Pulmonary gas exchange status is best evaluated by the integrated reading of P_{aO_2} and P_{aCO_2}.
- A–B status is best evaluated by the integrated reading of P_{aCO_2} and pH, with concomitant measurement of serum electrolytes.
- Mixed A–B disorders are very common in clinical practice.
- The correct interpolation of ABG represents a fundamental step for the diagnosis and treatment of A–B disorders.
- The study of serum chloride is fundamental to further investigate the causes of metabolic disorders.

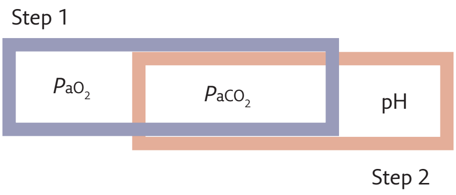


Figure 1. 'Two-step' approach to ABG interpretation.

particularly chloride (Cl^-), are measured, a further insight into the differential diagnosis of metabolic A–B disorders can be obtained (third step).

Step 1: evaluation of lung gas exchange

Healthy subjects at sea level breathing room air (inspired oxygen fraction (F_{IO_2}) 0.21) show P_{aO_2} values close to 90–95 mmHg (12.0–12.7 kPa). P_{aO_2} values <80 mmHg (<10.7 kPa) are considered arterial hypoxaemia and P_{aO_2} <60 mmHg (<8.0 kPa) indicates hypoxaemic respiratory failure. Because of the characteristics of the oxyhaemoglobin dissociation curve, a P_{aO_2} of 60 mmHg corresponds to a S_{aO_2} of ~90% and is located at the upper end of the steepest portion of the curve. P_{aO_2} values <60 mmHg will have a substantial impact, reducing arterial O_2 content and compromising tissue oxygenation. The accepted reference interval for P_{aCO_2} is 35–45 mmHg (4.7–6.0 kPa). By convention, hypercapnic respiratory failure is established at P_{aCO_2} >50 mmHg (>6.7 kPa).

Abnormal respiratory gases in arterial blood are generally due to impaired pulmonary gas exchange. Intrapulmonary factors that may cause arterial hypoxaemia are listed in table 1. Pulmonary ventilation (V'_A)/perfusion (Q') inequality is the most frequent determinant of hypoxaemia and hypercapnia in the clinical scenario. However, the identification of pulmonary shunt (perfusion of unventilated pulmonary units, $V'_A/Q'=0$) as main cause of hypoxaemia in a patient with severe pneumonia has relevant therapeutic implications. It is of note, however, that alterations of extrapulmonary factors such as cardiac output, F_{IO_2}, V'_{O_2}, and V'_E are also determinants of P_{aO_2} and P_{aCO_2}.

When P_{aCO_2} values are close to 40 mmHg (5.3 kPa), P_{aO_2} is an excellent indicator of the efficacy of the lung as O_2 exchanger, but abnormal P_{aCO_2} values (hypercapnia or hypocapnia) may benefit from the integrated reading of P_{aO_2} and P_{aCO_2} values indicated in table 1. Such an integrated view can be numerically obtained by computing the alveolar–arterial oxygen tension gradient (P_{A-aO_2}) using the following simplified formula:

$$P_{A-aO_2} = \left(\left(P_B - P_{H_2O} \right) F_{IO_2} - \frac{P_{aCO_2}}{R} \right) - P_{aO_2}$$

where P_B is barometric pressure, P_{H_2O} is airway water vapour partial pressure and R is the respiratory quotient (the ratio between the V'_{CO_2} and V'_{O_2}, ~0.80 at rest).

At sea level, the normal expected P_{A-aO_2} value is <15 mmHg (<2.0 kPa) in young subjects and <20 mmHg (<2.7 kPa) in the elderly. Table 1 shows the contribution of the P_{A-aO_2} to the identification of the mechanisms of alteration of ABG.

To further understand the cause of arterial hypoxaemia, the effect of supplemental oxygen breathing on P_{aO_2} should be examined, keeping in mind that in the normal lung P_{A-aO_2} widens when breathing additional oxygen. While hypoxaemia due to

Table 1. $P_{\mathrm{A-aO_2}}$ in the evaluation of the causes of arterial hypoxaemia

Cause	$P_{\mathrm{aO_2}}$	$P_{\mathrm{aCO_2}}$	$P_{\mathrm{A-aO_2}}$
Hypoventilation	↓	↑	↔
V'_{A}/Q' mismatch	↓	↔↓↑	↑
O_2 diffusion limitation	↓	↔↓	↑
Shunt	↓↓	↔↓↑	↑↑

pulmonary V'_{A}/Q' inequalities and diffusion defects is usually corrected by increasing inspired O_2 concentrations, this does not correct respiratory failure due to shunt.

A simple, but less accurate, way to compute $P_{\mathrm{A-aO_2}}$ is to use the rule of '130'. It is assumed that in a healthy subject, at sea level ($F_{\mathrm{IO_2}}=0.21$), the sum of $P_{\mathrm{aO_2}}$ and $P_{\mathrm{aCO_2}}$ should be ~130 mmHg (~17.3 kPa). Consequently, the difference between 130 and the $P_{\mathrm{aO_2}}+P_{\mathrm{aCO_2}}$ is a surrogate of $P_{\mathrm{A-aO_2}}$. The following examples illustrate the reader on the use of the rule.

- A patient with $P_{\mathrm{aO_2}}$ 70 mmHg (9.3 kPa) and $P_{\mathrm{aCO_2}}$ 60 mmHg (8.0 kPa) (130–(70+60)=0 mmHg) is hypoventilating a lung that is functionally 'normal', with a $P_{\mathrm{A-aO_2}}$ within the reference interval.
- However, a patient with hypoxaemic respiratory failure and hypocapnia (130–($P_{\mathrm{aO_2}}$ 50+$P_{\mathrm{aCO_2}}$ 20)=60 mmHg (8.0 kPa)) shows worse pulmonary O_2 exchange (higher $P_{\mathrm{A-aO_2}}$) than a patient with respiratory failure and hypercapnia (130–(50+50)=30 mmHg (4.0k Pa)).

The computation of $P_{\mathrm{A-aO_2}}$ (and the use of the rule of 130) is not useful clinically when $F_{\mathrm{IO_2}}$ increases. Calculating the $P_{\mathrm{aO_2}}/F_{\mathrm{IO_2}}$ ratio is recommended to assess the efficacy of the lung as an O_2 exchanger in critical care when comparing ABG measurements taken at different $F_{\mathrm{IO_2}}$ values. Lung injury is defined as $P_{\mathrm{aO_2}}/F_{\mathrm{IO_2}}$ <300 while acute respiratory distress syndrome (ARDS) is associated with $P_{\mathrm{aO_2}}/F_{\mathrm{IO_2}}$ <200 (table 2).

Table 2. Respiratory failure

Hypoxaemic respiratory failure

- $P_{\mathrm{aO_2}}$ ≤60 mmHg (≤8.0 kPa) and $P_{\mathrm{aCO_2}}$ normal or low, at sea level ($F_{\mathrm{IO_2}}=0.21$)
    - Hypoxaemia due to pulmonary V'_{A}/Q' mismatching ($P_{\mathrm{aO_2}}$ enhances with $F_{\mathrm{IO_2}}$)
        - Chronic respiratory diseases (only pulmonary fibrosis shows O_2 diffusion limitation together with V'_{A}/Q' mismatching)
    - Hypoxaemia due to intrapulmonary shunt (lung units with $V'_{\mathrm{A}}/Q'=0$) ($P_{\mathrm{aO_2}}$ does respond to $F_{\mathrm{IO_2}}$) ($P_{\mathrm{aO_2}}/F_{\mathrm{IO_2}}$ ≤200 mmHg (≤26.7 kPa))
        - ARDS

Hypercapnic respiratory failure

- $P_{\mathrm{aCO_2}}$ ≤50 mmHg (≤6.7 kPa) and $P_{\mathrm{aO_2}}$ low, at sea level ($F_{\mathrm{IO_2}}=0.21$)
    - 'Normal' lung ($P_{\mathrm{A-aO_2}}$ preserved)
        - Reduced alveolar ventilation due to extrapulmonary factor
- Advanced chronic respiratory disease or severe exacerbation
    - Hypoxaemia due to pulmonary V'_{A}/Q' mismatching

Recently, three mutually exclusive categories of ARDS based on degree of hypoxsemia has been proposed:

- Mild (P_{aO_2}/F_{IO_2} 200–≤300 mmHg (26.7–≤40 kPa))
- Moderate (P_{aO_2}/F_{IO_2} 100–≤200 mmHg (13.3–≤26.7 kPa))
- Severe (P_{aO_2}/F_{IO_2} ≤100 mmHg (≤13.3 kPa))

Step 2: diagnosis of A–B disorders

Arterial pH is highly regulated to be maintained between 7.38 and 7.42. In the clinical assessment of A–B equilibrium, two main determinants of arterial pH must be taken into account, namely:

- the respiratory component (P_{aCO_2})
- the metabolic component

Hypercapnia (high P_{aCO_2}) generates respiratory acidosis (low pH) whereas hypocapnia (low P_{aCO_2}) is associated to respiratory alkalosis (high pH). In simple acute respiratory disorders, for each 10-mmHg (1.3-kPa) variation in P_{aCO_2}, the expected change in pH value is 0.07 for acidosis and 0.08 for alkalosis, while in simple chronic respiratory disorders, it is 0.03 for both acidosis and alkalosis.

The metabolic component refers to the impact of nonvolatile molecules generating acidosis or alkalosis. The variable most often used to assess the metabolic component is bicarbonate concentration ($[HCO_3^-]$) computed through the Henderson–Hasselbalch equation:

$$\mathrm{pH} = 6.1 + \log\left(\frac{[\mathrm{HCO_3^-}]}{0.03P_{\mathrm{CO_2}}}\right)$$

In the past, the role of simple rules associating changes in P_{aCO_2} with changes in pH (and HCO_3^-) has been emphasised as useful for the diagnosis of simple and mixed A–B disorders. A graphical illustration of this approach in indicated in figure 2.

Table 3 displays some examples of simple A–B disorders. The first two rows in table 3 indicate simple, uncompensated A–B disorders. The first row may correspond to a COPD patient with an episode of severe exacerbation showing acute hypercapnia leading to respiratory acidosis. The second example fits with any situation leading to hyperventilation and low P_{aCO_2} that generates respiratory alkalosis (*e.g.* interstitial oedema in HF). The third row indicates an example of acidosis due to a metabolic disturbance (*e.g.* exercise-related increase in blood lactate, ketoacidosis or renal failure). Finally, the fourth example of A–B disequilibrium corresponds to a metabolic alkalosis that may be seen in patients with liquid depletion and low intracellular and serum potassium (K^+) concentrations (*e.g.* excessive diuretic therapy).

Common causes of A–B disorders are illustrated in tables 4 and 5. It is of note that although they may begin as simple disorders (respiratory or metabolic), they often evolve to mixed A–B abnormalities.

Step 3: more on A–B disorders

To further investigate the causes of metabolic disorders, the measurement of serum electrolytes, and particularly Cl^-, is of great help. While respiratory disturbances directly affect pH by modifying P_{aCO_2}, metabolic disturbances derive from changes in the net difference between negative and positive charges dissolved in the serum

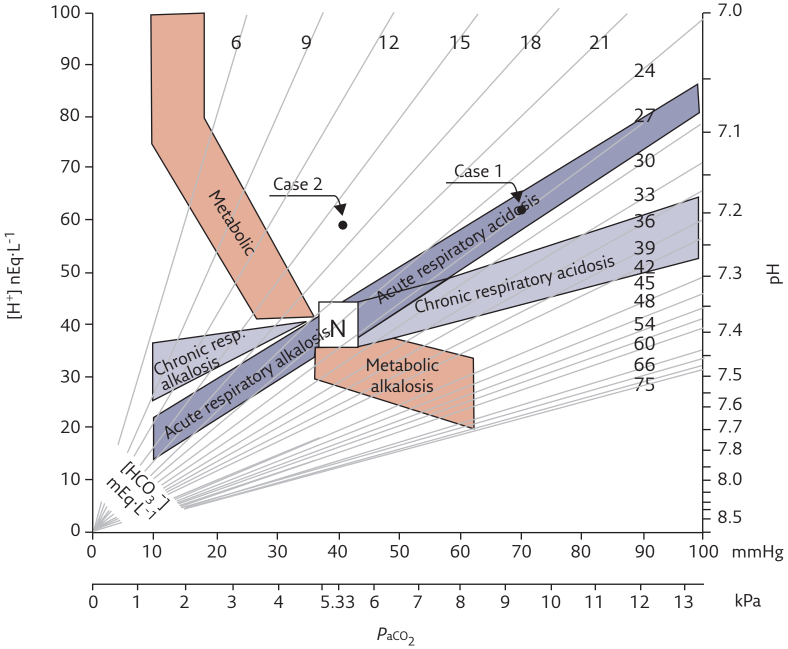


Figure 2. P_{aCO_2}*–pH nomogram for the diagnosis of A–B disorders.* P_{aCO_2}*–pH values that fall into the acute or chronic, respiratory and nonrespiratory (or metabolic) 'bands' should be considered as 'simple' disorders (case 1:* P_{aCO_2} *70 mmHg (9.3 kPa), pH 7.19; acute respiratory acidosis).* P_{aCO_2}*–pH values that fall between the respiratory and metabolic bands should be considered as 'mixed' disorders (case 2:* P_{aCO_2} *40 mmHg (5.3 kPa), pH 7.20; acute respiratory and metabolic acidosis). Reproduced and modified from Goldberg et al. (1973) JAMA; 223: 269–275, with permission from the publisher.*

(strong ions and weak acids). The increase in negative charges reduces pH while their reduction increases pH. The negative charges that strongly influence the A–B equilibrium are Cl^- and the so called nonmeasurable anions (see later). Several types of renal tubular acidosis impair renal Cl^- excretion, resulting in a net increase in serum Cl^- concentration and thus in metabolic acidosis. Lower gastrointestinal losses of sodium (Na^+), K^+ and water (diarrhoea) cause an increase in the serum concentration of Cl^-, resulting in hyperchloraemic acidosis. However, reduction of Cl^- (*e.g.* loop diuretics) and loss of NaCl (*e.g.* diarrhoea in small bladder diseases) can cause metabolic alkalosis. The reason why loss of Cl^- and Na^+ generates A–B disturbance can be understood only considering the vasopressin/thirst system that acts in parallel with other systems (*e.g.* aldosterone or ammonium (NH_4^+) secretion), regulating

Table 3. Examples of simple A–B disorders

	pH	P_{aCO_2}	$[HCO_3^-]$
Respiratory acidosis	↓	↑	↔
Respiratory alkalosis	↑	↓	↔
Metabolic acidosis	↓	↓	↓
Metabolic alkalosis	↑	↑	↑

Table 4. Respiratory disorders

Respiratory acidosis	
	Central nervous system depression, neuromuscular disorders
	Chest wall abnormalities
	Lung diseases
Respiratory alkalosis	
	Anxiety, central nervous system disorders
	Hormones, drugs (catecholamine, progesterone, hyperthyroidism, salicylate)
	Fever
	Hypoxia
	Liver diseases

free water renal excretion in order to maintain plasma osmolarity. For simplicity, consider a situation in which the only strong ions in the plasma are Na^+ and Cl^- (with concentrations of 140 and 100 $mEq \cdot L^{-1}$) and the remaining negative charges are only represented by HCO_3^- (figure 3). If only Na^+ is lost in the form of $NaHCO_3$ (figure 3a), the resulting hyponatraemia and hypo-osmolarity inhibits vasopressin secretion, generating water loss, and brings $[Na^+]$ back to the initial value (140 $mEq \cdot L^{-1}$). Cl^- will be concentrated by the same proportion as $[Na^+]$, leading to a net increase in $[Cl^-]$.

If Na^+ and Cl^- are lost in form of NaCl (figure 3b), with inadequate salt reintegration, their plasma concentrations will be reduced by the same, amount causing

Table 5. Metabolic disorders

Metabolic acidosis		
	Normochloraemic acidosis (high anion gap acidosis)	
		Ketoacidosis
		Lactic acidosis
		Renal failure
		Toxins
	Hyperchloraemic acidosis (normal anion gap acidosis)	
		Extrarenal loss of Na^+
		Renal tubular acidosis
Metabolic alkalosis		
	Cl^--responsive type	
		Gastric fluid loss
		Volume contraction
	Cl^--resistant type	
		Mineralocorticoid disorders
		Milk-alkali syndrome, Bartter syndrome
		Hypoalbuminaemia

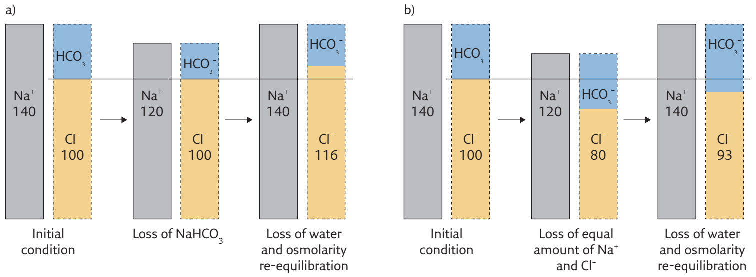

a)
b)
Na⁺ 140
HCO3⁻
Cl⁻ 100
Na⁺ 120
Cl⁻ 116
Cl⁻ 80
Cl⁻ 93
Initial condition
Loss of NaHCO3
Loss of water and osmolarity re-equilibration
Loss of equal amount of Na⁺ and Cl⁻

Figure 3. Why the loss of Cl^- and Na^+ in equal quantities reduces plasma Cl^- concentration. a) Loss of Na^+ generates a net increase in $[Cl^-]$ and metabolic hyperchloraemic acidosis, while b) loss of Na^+ and Cl^- causes a net reduction in $[Cl^-]$ and metabolic alkalosis (see main text for details). Concentrations are given in milliequivalents per litre.

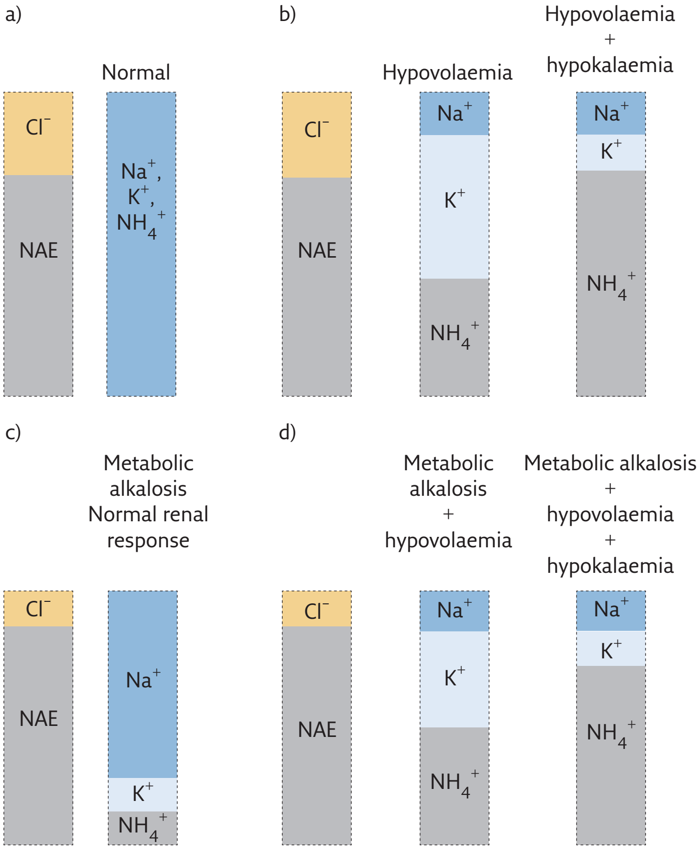

a)
Normal
Cl⁻
NAE
Na⁺, K⁺, NH4⁺
b)
Hypovolaemia
Hypovolaemia + hypokalaemia
Na⁺
K⁺
NH4⁺
c)
Metabolic alkalosis Normal renal response
d)
Metabolic alkalosis + hypovolaemia
Metabolic alkalosis + hypovolaemia + hypokalaemia

Figure 4. Role of renal ammoniagenesis in metabolic alkalosis maintenance. Renal excretion of negative and positive urinary ions under conditions of a) normal A–B equilibrium and c) in response to metabolic alkalosis. b and d) The same A–B equilibria in the presence of hypovolaemia and hypokalaemia (see main text for details).

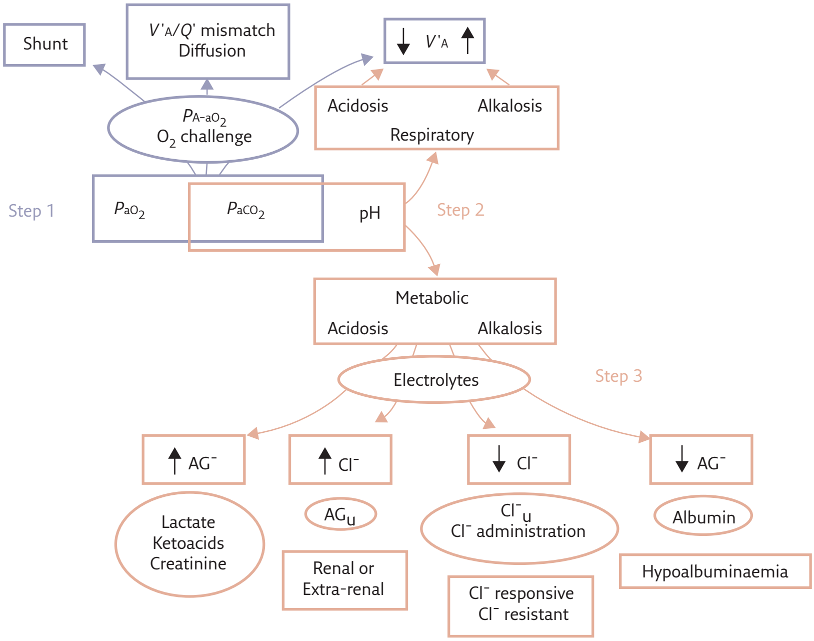

Shunt
V'A/Q' mismatch
Diffusion
V'A
PA-aO2
O2 challenge
Acidosis
Alkalosis
Respiratory
Step 1
PaO2
PaCO2
pH
Step 2
Metabolic
Acidosis
Alkalosis
Electrolytes
Step 3
AG−
Cl−
Cl−
AG−
Lactate
Ketoacids
Creatinine
AGu
Renal or
Extra-renal
Cl−u
Cl− administration
Cl− responsive
Cl− resistant
Albumin
Hypoalbuminaemia

Figure 5. Comprehensive approach to ABG interpretation. $_u$: urinary.

hyponatraemia and hypochloraemia (*e.g.* $[Na^+]=140-20=120$ mEq·L^{-1}, $[Cl^-]=100-20=80$ mEq·L^{-1}). The response of vasopressin system again generates water loss that brings $[Na^+]$ back to the initial value (140 mEq·L^{-1}) and concentrates Cl^- by the same proportion as Na^+; however, in this case, this leads to a net reduction in $[Cl^-]$ ($(140/120) \times 80=93.3$ mEq·L^{-1}), generating metabolic alkalosis.

The main renal mechanism that may cause metabolic alkalosis is the rise in renal ammoniagenesis that stimulates Cl^- excretion as NH_4Cl. Several factors can increase renal ammoniagenesis: primary hyperaldosteronism, hypovolaemia (*e.g.* secondary hyperaldosteronism) and hypokalaemia. The body synthesises nonvolatile acids (negative charges in solution) that must be excreted by the kidney every day (*i.e.* net acid excretion (NAE)) in salt form (*i.e.* paired with a cation). There are three main cations that can pair with the NAE: Na^+, K^+ and NH_4^+ (figure 4a). When the body needs to retain Na^+ (hypovolaemia) or K^+ (hypokalaemia), ammoniagenesis increases and the main cation excreted with NAE is NH_4^+ (figure 4b). The normal kidney response during metabolic alkalosis is the reduction of ammoniagenesis in order to excrete more Na^+ than Cl^- (figure 4c), increasing the serum $[Cl^-]$ by the mechanism described earlier. However, in the presence of conditions that require Na^+ and K^+ retention, increased NH_4^+ excretion avoids the correction of metabolic alkalosis (figure 4d).

The comprehension of this mechanism is fundamental to understanding the causes of persistent metabolic alkalosis in order to provide the correct treatment. Protracted vomiting is the typical situation in which this mechanism is present: the initial condition causes loss of Cl^- without Na^+ and the hypovolaemia prevents the correction of alkalosis; volume reintegration will be sufficient to correct metabolic alkalosis. In the clinical setting, the causes of metabolic alkalosis can be classified as Cl^--responsive or volume-responsive and Cl^--resistant or volume-resistant based on the response to the Cl^- salt administration and volume reintegration (table 5).

Negative charges other than Cl^- are usually calculated by the anion gap (AG^-) formula:

$$AG^- = [Na^+] - ([Cl^-] + [HCO_3^-])$$

The AG^- represent the amount of nonmeasurable anions (acids) and the normal value is ~12–14 $mEq \cdot L^{-1}$. The most common acids that cause high-AG^- metabolic acidosis are lactic acid (lactic acidosis), ketoacids (diabetic or alcoholic acidosis) and inorganic acids (renal failure). Reduction in AG^- due to severe reduction in serum albumin can generate a mild metabolic alkalosis.

Conclusion

In clinical practice, the correct interpretation of ABG provides unique information on the characteristics and severity of lung gas exchange impairment, and on A–B abnormalities. It represents a fundamental step towards an appropriate diagnosis of the patient and the adoption of the treatment strategy. Figure 5 summarises the interpretative 'integrative' approach to be used in the evaluation of the ABG. As a first step (step 1), the combined reading of P_{aO_2} and P_{aCO_2} values, on room air and during supplemental oxygen breathing, should be used to identify the causes and the severity of arterial hypoxaemia (blue squares and blue circles). As a second step (step 2), the combined reading of P_{aCO_2} and pH is needed for the correct diagnosis of A–B disorders (red squares). Furthermore, the study of serum electrolytes, particularly Cl^-, may be of great help in the identification of the causes of metabolic disorders (red squares) (step 3).

Further reading

- ARDS Definition Task Force (2012). Acute respiratory distress syndrome: the Berlin Definition. *JAMA*; 307: 2526–2533.
- Astrup P (1956). A simple electrometric technique for the determination of carbon dioxide tension in blood and plasma, total content of carbon dioxide in plasma and bicarbonate content in 'separated' plasma at fixed carbon dioxide tension. *Scand J Clin Lab Invest*; 8: 33.
- Brackett NC Jr, *et al.* (1965). Carbon dioxide titration curve of normal man. Effect of increasing degrees of acute hypercapnia on acid-base equilibrium. *N Engl J Med*; 272: 6–12.
- Hughes JMB (1999). Pulmonary gas exchange. In: Hughes JMB, *et al.*, eds. Lung Function Tests: Physical Principles and Clinical Applications. London, W.B. Saunders; pp. 75–92.
- Kassirer JP, *et al.* (1965). Rapid estimation of plasma carbon dioxide tension from pH and total carbon dioxide content. *N Engl J Med*; 272: 1067–1068.
- Kellum JA (2005). Reunification of acid–base physiology. *Crit Care*; 9: 500–506.
- Kellum JA (2007). Disorders of acid–base balance. *Crit Care Med*; 35: 2630–2606.
- Narins RG, *et al.* (1980). Simple and mixed acid-base disorders: a practical approach. *Medicine*; 59: 161–187.
- Roca J, *et al.* (1994). Principles and information content of the multiple inert gas elimination technique. *Thorax*; 49: 815–824.
- Riley RL, *et al.* (1949). 'Ideal' alveolar air and the analysis of ventilation–perfusion relationships in the lungs. *J Appl Physiol*; 1: 825–847.

- Riley RL, *et al.* (1951). Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs: theory. *J Appl Physiol*; 4: 77–101.
- Severinghaus JW, *et al.* (1958). Electrodes of blood P_{O_2} and P_{CO_2} determination. *J Appl Physiol*; 13: 515–520.
- Stewart PA (1983). Modern quantitative acid–base chemistry. *Can J Physiol Pharmacol*; 61: 1444–1461.
- Wagner PD (2008). The biology of oxygen. *Eur Respir J*; 31: 887–890.
- West JB (1971). Causes of carbon dioxide retention in lung disease. *N Engl J Med*; 284: 1232–1236.

Exercise testing

Paolo Palange and Paolo Onorati

The ability to exercise largely depends on the integrated physiological responses of the respiratory, cardiovascular and skeletal muscle systems. In healthy individuals, exercise tolerance is influenced by age, sex and level of fitness. In patients with lung and heart diseases, exercise tolerance is typically reduced and limited by symptoms such as dyspnoea and leg fatigue.

Cardiopulmonary exercise testing (CPET), *i.e.* the study of ventilatory, cardiovascular and pulmonary gas exchange variables during symptom-limited incremental exercise, is considered the 'gold standard' for evaluating the degree and the causes of exercise intolerance in disease states. Moreover, CPET has been extensively used in patients with COPD, CF, interstitial lung diseases (ILDs), pulmonary vascular disorders (PVDs) and CHF. In COPD and CF, exercise tolerance is mainly limited by pulmonary mechanic abnormalities (*e.g.* reduction in ventilatory capacity or dynamic hyperinflation). In ILD, exercise tolerance is limited by ventilatory constraints and pulmonary gas exchange abnormalities (*e.g.* arterial oxygen desaturation). In PVDs and CHFs both circulatory (*e.g.* reduced adaptation in cardiac output) and pulmonary gas exchange abnormalities contribute to exercise intolerance (table 1). Notably, in the early phases of respiratory diseases, even in the presence of normal spirometry, CPET may reveal signs of reduced lung gas exchange efficiency (*i.e.* increased V'_E for a given carbon dioxide output (V'_{CO_2})).

Exercise protocols

Maximal incremental test

The symptom-limited maximal incremental exercise protocol is recommended as a first step in the evaluation of exercise tolerance. V'_E, heart rate (HR), O_2 uptake (V'_{O_2}), V'_{CO_2}, and end-tidal O_2 and carbon dioxide are the primary variables measured, typically on a breath-by-breath basis using computerised systems. Additional required measurements include ECG, blood pressure, dyspnoea, leg discomfort, exercise-related arterial O_2 desaturation and flow–volume loop recording. Careful selection of

Key points

Cardiopulmonary exercise testing is considered the gold standard for:

- An objective measure of exercise capacity
- Identifying the mechanisms limiting exercise tolerance
- Establishing indices of the patient's prognosis
- Evaluating the effects of therapeutic interventions

Table 1. Causes of exercise intolerance in lung diseases

Ventilatory limitation to exercise
Reduced ventilatory efficiency
Dynamic hyperinflation
Increased work of breathing
Pulmonary gas exchange abnormalities
Excessive perception of symptoms
Impaired cardiovascular response to exercise and reduced oxygen delivery
Peripheral muscle weakness/dysfunction

patients minimises the likelihood of serious complications during maximal incremental exercise testing. Myocardial infarction (within 3–5 days), unstable angina, severe arrhythmias, pulmonary embolism, dissecting aneurism and severe aortic stenosis represent absolute contraindications to CPET. Resting lung function measurement and ECG are usually obtained before CPET. Cycle and treadmill exercise have been utilised interchangeably, although the former is largely used as the work rate for incremental and endurance tests is easier to quantify. As the exercise period should last 10–12 min, the work rate increment should be selected carefully. In patients with lung diseases, the usual rate of workload increase is 10 $W \cdot min^{-1}$, although slower or faster rates are possible in the very sick and in fitter patients, respectively. The maximal incremental exercise test is also utilised to determine the appropriate work rate to be used in an endurance protocol.

Constant work rate tests

Constant work rate (CWR) tests on a cycle ergometer or on a treadmill are used for the measurement of exercise 'endurance' tolerance and ventilatory and pulmonary gas exchange kinetics. CWR exercise results in steady-state responses when the work rate is of moderate intensity (*i.e.* below the lactate threshold (θ_L)); conversely, high-intensity CWR exercise (*i.e.* $>\theta_L$) results in steady states either being delayed or not attained at all.

Walking tests

Walking tests, such as the 6-min walking test (6MWT), have been increasingly used for the assessment of exercise tolerance in chronic lung diseases. The object of this test is to walk as far as possible in 6 min. The test should be performed indoors along a 30-m, flat, straight corridor; encouragement significantly increases the distance walked. Measurements of S_{pO_2}, HR and exertional symptoms are recommended during the 6MWT. Many important physiological measurements are not obtained unless a portable gas exchange telemetric device is used.

Indications for CPET

In patients with lung diseases, exercise testing is mainly used for functional and prognostic purposes. Other indications include detection of exercise-induced bronchoconstriction, selection of candidates for surgery including lung transplant and evaluation of the effects of therapeutic intervention including pulmonary rehabilitation.

Exercise variables and indices

Peak V'_{O_2}

The classical criterion for defining exercise intolerance and classifying degrees of impairment is the peak O_2 uptake (V'_{O_2peak}). With good subject effort on an incremental test, V'_{O_2peak} reflects a subject's maximal aerobic capacity ('maximum' V'_{O_2}). This index is taken to reflect the attainment of a limitation in the O_2 conductance pathway from the lungs to the mitochondria. Values <80% predicted are considered abnormal while values <40% predicted indicate severe impairment.

Lactate threshold

θ_L is the highest V'_{O_2} at which arterial lactate is not systematically increased, and is estimated using an incremental test. It is considered an important functional demarcator of exercise intensity. Sub-θ_L work rates can normally be sustained for prolonged periods. θ_L is dependent on age, sex, body mass and fitness. Noninvasive estimation of θ_L requires the demonstration of an augmented V'_{CO_2} in excess of that produced by aerobic metabolism, and its associated ventilatory sequelae.

Oxygen pulse

The O_2 pulse is the product of the stroke volume and the difference between the arterial (C_{aO_2}) and mixed venous O_2 contents (C_{vO_2}). Given the Fick equation:

$$V'_{O_2} = \text{cardiac output} \times (C_{aO_2} - C_{vO_2})$$

the O_2 pulse can be calculated as:

$$O_2 \text{ pulse} = \frac{V'_{O_2}}{HR}$$

In patients with ILD, the O_2 pulse at peak exercise is lower, and its rate of increase with increasing work rate is usually reduced because of the reductions in stroke volume and C_{aO_2}. In PVDs, the O_2 pulse is characteristically low at peak exercise and may not increase during incremental exercise, reflecting the abnormal cardiac output adaptation.

Heart rate reserve

The peak heart rate (HR_{peak}) achieved in a symptom-limited exercise test decreases with age. The most commonly used equation to predict HR_{peak} is:

$$HR_{peak_{pred}} = 220 - \text{age}$$

Heart rate reserve (HRR) is defined as the difference between $HR_{peak_{pred}}$ and HR_{peak}. In healthy individuals, HHR is virtually zero; a high HRR is usually observed in patients with COPD, CF or ILD.

Ventilatory efficiency: V'_E/V'_{CO_2} slope and intercept

It is conventional to express the ventilatory response to exercise relative to V'_{CO_2} (figure 1). It can be measured as the slope of the V'_E–V'_{CO_2} relationship ($\Delta V'_E/\Delta V'_{CO_2}$) over its linear region, *i.e.* typically extending from 'unloaded pedalling' to the respiratory compensation point (RCP). In normal individuals, $\Delta V'_E/\Delta V'_{CO_2}$ values of ~23–25 have been reported; values >32 are considered abnormal. Ventilatory efficiency during exercise may also be expressed by the ratio V'_E/V'_{CO_2} that represents the litres of ventilation necessary to clear 1 L CO_2. Up to the RCP, V'_E/V'_{CO_2} declines curvilinearly as work rate increases. It is common practice to record the value at θ_L ($V'_E/V'_{CO_2}@\theta_L$) or the minimum value (V'_E/V'_{CO_2} nadir). Several factors may increase $\Delta V'_E/\Delta V'_{CO_2}$ slope and $V'_E/V'_{CO_2}@\theta_L$, such as hypoxaemia, acidosis, increased levels of wasted ventilation and pulmonary hypertension. Of note is that ventilatory efficiency is often reduced in

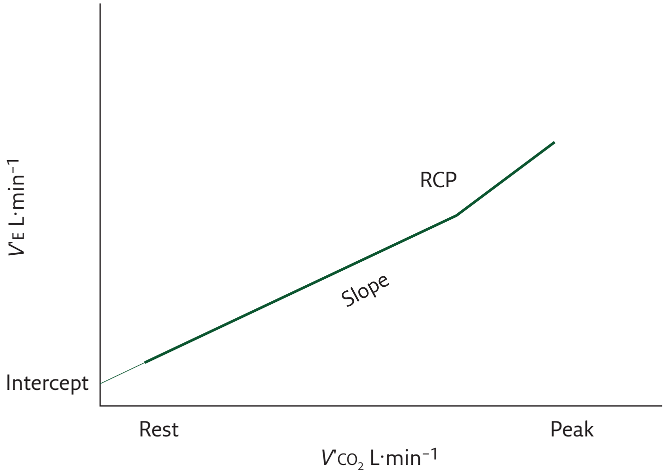


Figure 1. Ventilatory efficiency during CPET in a normal subject.

the early phases of respiratory (*e.g.* COPD) and cardiovascular (*e.g.* CHF) diseases. The 'intercept' of the V'_E/V'_{CO_2} slope on the V'_E-axis (~4 L·min^{-1} in normal individuals) has been recently recognised as marker of increased levels of wasted ventilation in COPD and emphysema (when >8 L·min^{-1}); in moderate to severe, pulmonary hypertension the intercept is often negative.

Breathing reserve

Breathing reserve (BR) provides an index of the proximity of the ventilation at the limit of tolerance ($V'_{E_{max}}$) to the maximal achievable ventilation (MVV) (estimated as the subject's resting $FEV_1 \times 40$). BR can be defined as $V'_{E_{max}}$ as a percentage of MVV:

$$BR = 1 - \frac{V'_{E_{max}}}{MVV}$$

In COPD, CF and ILD, BR is usually reduced or absent at peak CPET exercise.

Dynamic hyperinflation

Changes in end-expiratory lung volume (EELV) during exercise can be estimated by asking the subject to perform an inspiratory capacity manoeuvre at a selected point in the exercise test. In normal subjects, EELV decreases with increasing work rate by as much as 0.5–1.0 L below functional residual capacity. In COPD, particularly in the advanced phases of the disease, EELV increases during exercise (*i.e.* dynamic hyperinflation) in spite of expiratory muscle activity. Dynamic hyperinflation is strongly associated with dyspnoea in patients with respiratory diseases.

Arterial O_2 desaturation

During exercise, S_{pO_2} is normally maintained in the region of ~97–98%. However, arterial O_2 desaturation can be observed in patients with moderate–severe ILD and in patients with primary pulmonary hypertension.

The tolerable limit of exercise and 'isotime' measurements

The tolerable limit of exercise (t_{LIM}) is expressed as function of time measured during CWR protocols. In clinical practice, high-intensity (~70–80% Watt max) CWR protocols are used for the evaluation of interventions. In addition to tLIM, measurement of pertinent physiological variables (*e.g.* V'_E, inspiratory capacity and dyspnoea) at standardised time (isotime) are obtained.

CPET response patterns

Ventilatory response

In normal individuals during incremental exercise, V'_E increases linearly relative to work rate, or V'_{O_2}. At some point, V'_E begins to increase more steeply in response to the development of lactic acidosis to maintain acid–base homeostasis (normal individual (blue lines) in figure 2). The ventilatory response to exercise in patients with lung disorders is increased (*i.e.* ventilation is higher at any given work rate) (COPD patient (red lines) in figure 2). Ventilatory limitation is commonly judged to occur when V'_E/MVV exceeds 85%. In lung diseases, the increase in V'_E/MVV may reflect a reduction in MVV but also an increase in V'_E. The ventilatory response during exercise is influenced by metabolic rate (V'_{CO_2}), P_{aCO_2} and the physiological dead space (V_D) fraction of the tidal volume (V_T). The relationship existing among these variables is described by the equation:

$$V'_E = \frac{863V'_{CO_2}}{P_{aCO_2}(1-\frac{V_D}{V_T})}$$

In lung diseases, for a given V'_{CO_2} and P_{aCO_2}, V'_E is usually increased because of a higher V_D/V_T. $\Delta V'_E/\Delta V'_{CO_2}$ or $V'_E/V'_{CO_2}@\theta_L$ are often used in the functional assessment of patients with lung diseases (*e.g.* COPD, ILD and PVDs) and cardiovascular disorders (*e.g.* CHF). V'_E/V'_{CO_2} is usually increased, particularly in patients with PVDs. Another particular behaviour of the V'_E response during exercise is the cyclic fluctuation of V'_E and expired gas kinetics, also defined as exertional oscillatory ventilation (EOV), which can occur in approximately one third of patients with CHF. While the origin of such a ventilatory abnormality is still controversial, its clinical relevance in terms of a negative prognosis is well established.

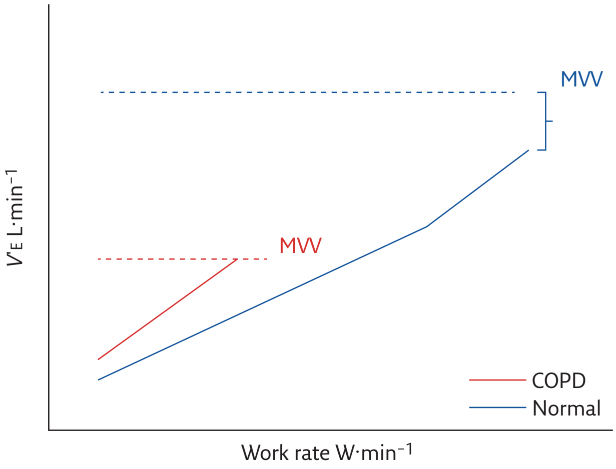


Figure 2. Ventilatory limitation to exercise in patients with COPD compared to normal subjects.

Pulmonary gas exchange

The efficiency of pulmonary gas exchange can be assessed by studying the magnitude of the alveolar–arterial O_2 tension difference (P_{A-aO_2}) at rest and during exercise. Normally, P_{aO_2} does not decrease during exercise and P_{A-aO_2} at peak exercise usually remains below 20–30 mmHg (2.7–4.0 kPa). In most patients with ILD or PVDs, pulmonary gas exchange efficiency is impaired, as indicated by an abnormally large P_{A-aO_2} (>30 mmHg, >4.0 kPa) at peak exercise accompanied by arterial O_2 desaturation. These changes reflect regional ventilation/perfusion ratio dispersion and alterations in pulmonary capillary transit time resulting from the recruited pulmonary capillary volume becoming inadequate for the high levels of pulmonary blood flow.

Cardiovascular response

CPET has proved very useful in the detection and quantification of cardiovascular abnormalities during exercise. The characteristic findings are a reduced V'_{O_2peak}, reduced θ_L, steeper HR–V'_{O_2} relationship (with a reduced HRR at peak exercise) and a shallower profile (or even flattening) of the O_2 pulse increase with increasing V'_{O_2}. An abnormal cardiovascular response to exercise is observed in PVDs and, in particular, in patients with idiopathic pulmonary arterial hypertension.

Exercise testing in prognostic evaluation

Exercise tolerance is well recognised as a valuable predictor of mortality in healthy subjects. This also appears to be the case in chronic pulmonary diseases. Exercise testing has become an essential component in the prognostic evaluation of patients with lung diseases (table 2).

Several studies have confirmed that V'_{O_2peak} is superior to other indices in the risk stratification of patients with end-stage lung diseases.

Evaluating the effects of therapeutic interventions

High-intensity (75–80% of peak work rate) endurance CWR protocols, performed on a cycle ergometer or on a treadmill, to tLIM have been successfully used in COPD patients for the evaluation of the effects of therapeutic interventions (*e.g.* bronchodilators, oxygen, heliox and rehabilitation). These types of protocols have a greater power of discrimination of therapy-induced changes in COPD patients, with a higher fractional improvement in exercise tolerance compared to incremental CPET. However, it must be considered that the hyperbolic profile of the relationship between the power output and exercise duration (tLIM) (power–duration curve) during CWR tests is responsible of the significant variability in the improvement magnitude of the tLIM. In fact, such an index is influenced by the pre-intervention work rate and exercise duration, and their relative positioning on subject's power–duration profile. Without knowledge of these aspects, any change in tLIM in a single CWR bout must be interpreted cautiously in terms of realistic physiological benefits obtained from the intervention.

Table 2. CPET prognostic indices

	COPD	ILD	CF	PVDs	CHF
↓V'_{O_2}peak	+	+	+	+	+
↑V'_E/V'_{CO_2}		+			++
Arterial O_2 desaturation		++	+	+	
EOV					++

Further reading

- ERS Task Force, *et al.* (2007). Recommendations on the use of exercise testing in clinical practice. *Eur Respir J*; 27: 529–541.
- ERS Task Force on Standardization of Clinical Exercise Testing (1997). Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. *Eur Respir J*; 10: 2662–2689.
- Johnson B, *et al.* (2003). ATS/ACCP Statement on Cardiopulmonary Exercise Testing. IV. Conceptual and physiologic basis of cardiopulmonary exercise testing measurements. *Am J Respir Crit Care Med*; 167: 228–238.
- Neder AJ, *et al.* (2017). Physiological and clinical relevance of exercise ventilatory efficiency in COPD. *Eur Respir J*; 49: 1602036.
- O'Donnell DE, *et al.* (2001). Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 164: 770–777.
- Palange P, *et al.* (2018). Clinical Exercise Testing (ERS Monograph). Sheffield, European Respiratory Society.
- Puente-Maestu L, *et al.* (2016). Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement. *Eur Respir J*; 47: 429–460.
- Wasserman K, *et al.* (2005). *Principles of Exercise Testing and Interpretation*, 4th Edn. Philadelphia, Lippincott Williams & Wilkins.
- Whipp BJ, *et al.* (2009). Quantifying intervention-related improvements in exercise tolerance. *Eur Respir J*; 33: 1254–1260.

Bronchial provocation testing

Frans de Jongh

To diagnose airway hyperreactivity, reversibility on a β_2-receptor agonist like salbutamol is the simplest and most commonly used test. If the lung function of a patient with an obstructive lung disease like asthma improves substantially on medication (normally an increase in FEV_1 >12% and 200 mL) bronchial hyperresponsiveness (BHR) is highly likely. However, if the patient did not inhale a substance that might trigger bronchoconstriction on the day of the measurement, their lung function might already be maximal, and so will not markedly improve after inhaling a β_2-agonist bronchodilator. BHR is defined as 'an increase in the ease and degree of airflow limitations in response to a bronchoconstrictor stimulus *in vivo*' (Sterk 1996). BHR can be assessed by several methods mainly divided into direct *versus* indirect tests. Direct tests involve a stimulus like methacholine (a neurotransmitter) or histamine (a mediator) which directly contracts the airway smooth muscle in the bronchial walls, which in turn might lower the FEV_1 of the patient. Indirect tests mostly involve a provocation which triggers a cascade of effects. For instance, airway walls might dry out due to hyperventilation thereby changing the osmolarity of the fluid lining these walls. This might release inflammatory mediators which may finally lead to the release of histamine. An overview of both the direct and indirect tests can be found in figure 1. The different tests will give different clinical information; thus, depending on the aim, a test should be chosen ranging from specific allergen provocation test to 'standard' methacholine provocation test. One should be aware that most indirect tests (*e.g.* exercise challenge tests) cannot be graded. That means that they will maximally provoke the airways of that patient during the test and can therefore induce a severe bronchoconstriction for patients with hyperactive lungs. One could compare it with a direct test (*e.g.* a metacholine test) in which one directly would start with the highest concentration of metacholine.

Key points

- Indirect challenge tests are more specific for asthma than direct challenge tests.
- Direct challenge tests are more sensitive than indirect tests, but not specific for asthma.
- When performing a direct challenge test, use a tidal breathing protocol and report the PD_{20} instead of the PC_{20}.
- Indirect tests can be 'maximal provocation' tests, such as exercise and eucapnic voluntary hyperventilation; or incremental tests, like mannitol, hypertonic or hypotonic aerosols or adenosine.

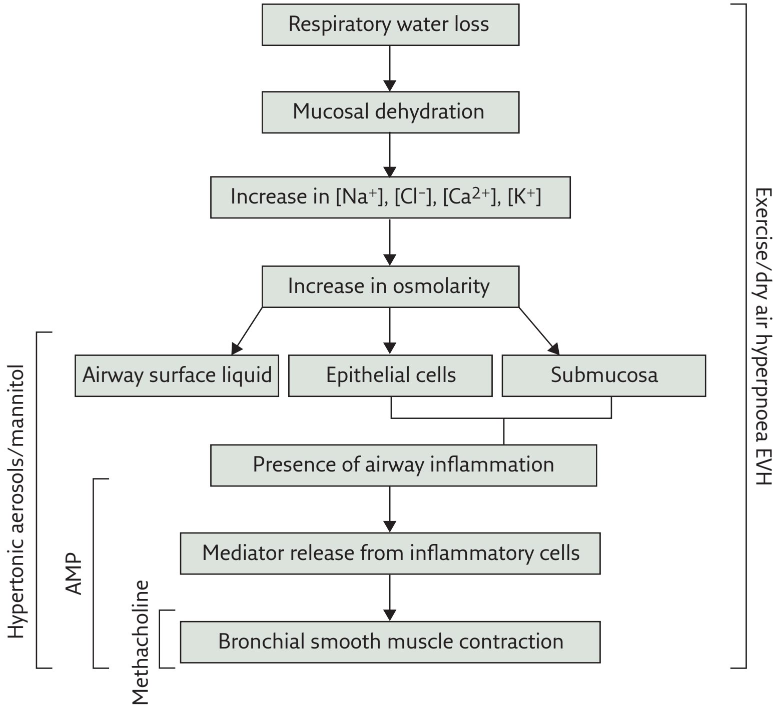

Respiratory water loss
Mucosal dehydration
Increase in [Na+], [Cl−], [Ca2+], [K+]
Increase in osmolarity
Airway surface liquid
Epithelial cells
Submucosa
Presence of airway inflammation
Mediator release from inflammatory cells
Bronchial smooth muscle contraction
Hypertonic aerosols/mannitol
AMP
Methacholine
Exercise/dry air hyperpnoea EVH

Figure 1. The cascade of effects when performing an (in)direct provocation test. Direct tests such as methacholine (or histamine) only affect bronchial smooth muscle contraction. An indirect test triggers more steps also finally leading to smooth muscle contraction. Reproduced from Anderson et al. *(2010).*

Direct provocation test

Recently, a European Respiratory Society task force (Coates *et al.*, 2017) published a technical standard for direct challenge tests endorsed by the American Thoracic Society. Standardisation of bronchial provocation tests is lacking worldwide. One problem is that most lung function labs work with nebulisers for methacholine or histamine as part of their up-to date spirometers. These nebulisers differ from those prescribed in the previous guidelines (Sterk *et al.*, 1993), simply because the old ones are not produced anymore. Another issue is that one can choose between a 2-min tidal breathing protocol for delivering the bronchoconstricting agent or a dosimeter method which gives an aerosol bolus when the patient takes a deep inhalation. When working with a dosimeter protocol the time of a test can be considerably reduced and being cheaper, it has gained popularity in past decades. Therefore, in clinical practice different kinds of nebulisers with varying settings were and are used and even the protocols used differed from centre to centre.

For these reasons the task force created a technical standard on bronchial challenge testing: ‘general considerations and performance of methacholine challenge tests’ (Coates *et al.*, 2017).

Contraindications for a direct provocation test are similar to those of indirect tests. These require conditions that patients should not be subject to any increased risk. This implies that the patient is also able to perform spirometry reliably. Since short-, long- and ultra-long acting β-agonist and anticholinergic agents, such as ipratropium bromide, may decrease airway hyperresponsiveness (AHR), these medications should be withheld for the appropriate working times before a test is performed. Preferably, methacholine is used which meets the criteria of Good Manufacturing Practices (methacholine chloride, trade name provocholine) to ensure quality, purity and consistency demands. By diluting with saline, a series of concentrations can be obtained for nebulisation. Preferably, a tidal breathing protocol is followed with at least 1-min nebulisation per step. Although modern, breath-actuated high output nebulisers could shorten nebulising time to 12 s; nebulising for at least 1 min (formerly 2 min) per step improves reproducibility. The characteristics of the nebuliser used (*e.g.* output rate and particle size) should match the concentrations and nebulising time and protocol followed. Using the provocative dose causing a fall in FEV$_1$ of 20% (PD$_{20}$) instead of the provocative concentration (PC$_{20}$) reduces the variability caused by using different nebulisers or nebulising protocols. Deep breaths should be avoided as much as possible since they change the bronchomotor tone. But deep breaths cannot be avoided since the test requires FEV$_1$ measurements. A tidal breathing protocol is therefore preferred and recommended. When using a dosimeter protocol, one should avoid inspirations up to TLC. For consistency of test results, it is essential that time of aerosol delivery and subsequent spirometry is standardised since there is a cumulative effect of methacholine. The fall in FEV$_1$ is still the standard outcome. Although resistance measurements by, for instance, body plethysmography or forced oscillation techniques might be more sensible, consistency and standardisation are considerably less compared to FEV$_1$ measurements. For interpretation, the scheme of Crapo *et al.* (2000) can be used (figure 2). One should estimate pre-test probability of asthma (*e.g.* 63%). When the PD$_{20}$ is 100 µg the post-test probability is 92%. When the PD$_{20}$ is 400 µg the PD$_{20}$ reduces to 24%. In general, the diagnostic value is optimal when the pre-test probability lies within 30% to 70%. The test is more useful in excluding a diagnosis of asthma then confirming it (Perpiná *et al*., 1993).

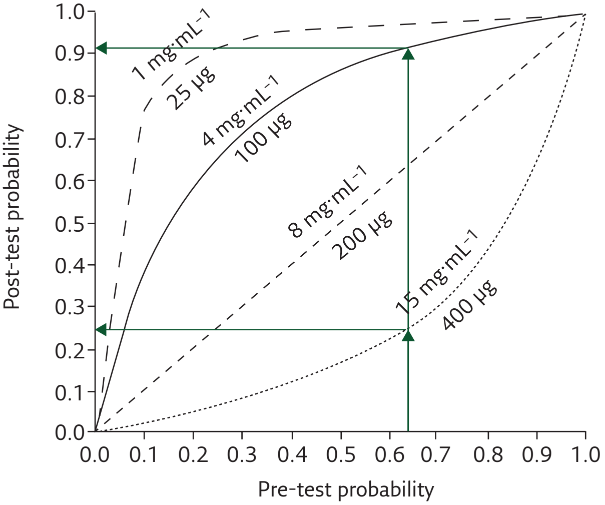


Figure 2. The relationship between pre- and post-test probability as well for the old standard (PC$_{20}$; mg·mL^{-1}) and new standard (PD$_{20}$; µg). Reproduced from Crapo et al. *(2010).*

Indirect provocation test

The same task force, which recently published guidelines for direct tests, also wrote a technical standard for indirect testing (Hallstrand *et al*., 2018). Indirect challenge tests are valuable tests to understand the underlying pathophysiology of asthma, since they trigger the same pathways by generating mediators from cells present in the airways. A well-known example is exercise-induced bronchoconstriction (EIB), which is common in asthmatic children. Although patients with asthma do not necessarily have EIB (there are many phenotypes) they will have AHR, so in general they have a positive direct challenge test. This means a direct challenge test can detect AHR but is not specific for asthma. To include or exclude the origin of the AHR an appropriate indirect provocation test is needed. However, caution is needed since several indirect challenge tests give an almost instantaneous maximal stimulus for bronchoconstriction (*e.g.* exercise challenge tests and eucapnic hyperventilation test) and therefore can lead to very severe bronchoconstriction. So, in many clinical situations a direct test is performed first. If the outcome is negative or borderline significant an indirect challenge test can be more safely performed and is more specific.

There are also graded challenge tests, such as mannitol, hypertonic saline and adenosine challenge test which are therefore safer, but frequently cost more. Allergen challenge tests are mostly used as a research tool in specialised centres. A subgroup of the task force, extended with experts on this topic, wrote a report on allergen challenge tests, which was endorsed by this task force (Diamant *et al*., 2013).

Indications

The prevalence of EIB in the general population might be around 10–18% while the prevalence of asthma is lower, indicating that not all patients with EIB have asthma. In particular, people routinely inhaling a lot of cold air might develop severe BHR. Cold air does not contain a lot of moisture so a high V'_{E} with cold/dry air will create a high osmotic stress in the airway epithelium which might release mediators provoking EIB.

The most common indication for an indirect challenge test is in paediatric asthma. Diagnosis and treatment might not only diminish dyspnoea complaints, but also prevent a sedentary lifestyle. Another relevant group of patients are people working in challenging or demanding environments like the military, police and firefighters. Another group are athletes since (inter-)national rules might demand a positive bronchial challenge test to admit the use of medication like (inhaled) corticosteroids, but rules on this have changed several times in past decades.

Exercise challenge test and eucapnic voluntary hyperventilation test

Exercise challenge tests are mostly performed on a motorised treadmill which ensures a rapid increase in V'_{E}. The target heart rate of ≥85% of maximal predicted heart rate, or if available a measured V'_{E} >60% of the mandatory minute ventilation (mostly approximated by 40×FEV1), should be obtained within 2–3 min. After reaching this the test should last another 6 min after which a series of spirometric measurements are performed at 0, 3, 6 10,15 and 30 min after exercise. If the FEV1 is not returned within 5% of baseline a β_2-agonist bronchodilator is given to restore the lung function to normal. Although some patients already show a lower FEV1 during exercise (breakthrough asthma) the lowest FEV1 is normally obtained 5 min after exercise.

The eucapnic voluntary hyperventilation (EVH) test is simpler since the patient does not have to exercise. But it is often more costly since the patient inhales several hundred litres of dry eucapnic (containing 4.9% carbon dioxide) medical gas for 6 min. Compared to exercise challenge testing it has a higher sensitivity.

Since exercise challenge tests and EVH tests deliver a maximal stimulus, all tests should be performed in a safe environment. Saturation is mostly monitored by pulse oximetry. ECG and blood pressure are also monitored when performing a test. The patient should be under close surveillance of the clinician or respiratory technician performing the test and adverse signs such as chest pain, severe wheezing, dyspnoea and lack of consciousness should be addressed appropriately. Trained personnel and good equipment to treat severe bronchoconstriction must be on site and cardiopulmonary resuscitation apparatus must be available.

It is recommended to test only when the FEV_1 in resting state is >75% of the reference value and oxygen saturation at rest is > 94%. Obtaining a stable value of the FEV_1 prior to the challenge test is therefore mandatory.

Both the exercise challenge test and the EVH test can also be conducted with cold air (–10 to –20°C) produced by a heat exchanger, or a cold air generator or in a cold environment like an ice-skating arena. Cold air makes the tests more sensitive. The preference is using a treadmill protocol while monitoring heart rate as surrogate for V'_E since heart rate is easier to measure than measuring V'_E. Although almost all pulmonary function labs will have an ergometer (*e.g.* for cardiopulmonary exercise tests), a motorised treadmill is preferred since it induces a rapid increase in ventilation while running. A fall in FEV_1 of ≥10% compared to baseline is considered to be a positive test for a population. If a higher specificity is required, which implies a lower sensitivity, a fall of ≥15% can be used to indicate a positive test.

Mannitol, hypertonic saline, adenosine and allergen challenge test

Exercise and EVH tests are indirect challenge tests which are close to what people might experience in daily life: a temporarily increased V'_E which dries the airways. However, these are maximal tests, that is, both tests give a maximal 'dose' to provoke bronchoconstriction. Mannitol, hypertonic or hypotonic and adenosine challenge test are all incremental tests in which the 'dose' is increased stepwise, with FEV_1 measurements between each dose, until the FEV_1 is decreased to a pre-set chosen value, normally 15%. Mannitol challenge tests have been studied extensively during the past decade as the product has regulatory approval worldwide. Mannitol, a strong osmotic agent, is inhaled as a dry powder aerosol with a high respirable fraction by means of a simple dry powder inhaler. After baseline spirometry a capsule is placed in the dry powder inhaler, pierced by pressing side-buttons and inhaled like most dry power inhalers require. If the subsequently measured FEV_1 does not fall >10% between two steps (or >15% compared to baseline) the next dose can be inhaled. In total, a maximum of (with steps 5, 10, 20, 40, 2×40, 3×40, 4×40 mg) 635 mg can be inhaled when FEV_1 remains stable. The big advantage of this test is, besides its incremental nature, the simplicity, both for the patient and the respiratory technician. Disadvantages might be severe coughing, often when patients inhale too fast (due to oropharyngeal deposition of the osmotic agent) and the costs of mannitol. The test outcome is given as PD_{15}, the provocative dose by which the FEV_1 is 15% lower than baseline. The PD_{15} can be used to classify AHR whereby AHR is mild if the PD_{15} is >155 mg, moderate if the PD_{15} is between 35 and 155 mg and severe if the PD_{15} is ≤35 mg. Studies with mannitol included studies for asthma screening, monitoring the effect of therapy on asthma and optimising asthma treatment.

Hypertonic challenge tests are normally conducted with increasing quantities of inhalation of aerosolised saline (4.5%) with a high output ultrasonic nebuliser.

Administration with a flow rate of at least 1.2 $\text{mL}\cdot\text{min}^{-1}$ is conducted for 30 s and 1, 2, 4 and 8 min as long as FEV_1 does not fall 15% lower than baseline. A PD_{15} of > 6 mL is considered to depict mild AHR. A PD_{15} of 2.1–6 mL is defined as moderate AHR and <2.1 mL as severe AHR. Again, a β_2-agonist is given if a PD_{15} is reached.

Adenosine (with adenosine 5′-monophospate (AMP)) and allergen challenge tests are normally only conducted for research and therefore beyond the scope of this chapter. Validated specific thresholds have not yet been found and non-uniformity (*e.g.* due to the change in muscle tone/protective effect of deep inspirations using a dosimeter protocol *versus* a tidal-breathing protocol) might be a reason for this. In addition, nebuliser characteristics like output rate and aerosol diameter produced make it hard to standardise AMP tests.

Direct tests are sensitive but not specific for asthma and therefore often used to rule-out airway hyperreactivity. Indirect tests are less sensitive but more specific and can therefore be used to discriminate asthma from other pulmonary pathologies. When using cold air during exercise challenge tests a sensitivity comparable to methacholine can be reached, while maintaining specificity (Carlsen *et al.* 1998). Another difference is that the outcomes of indirect tests are often affected within a week when taking (inhaled) corticosteroids, while the change in outcome of direct tests takes a few months. Measuring AHR when patients use medication might be of additional value. Sont *et al.* (1999) showed that asthma control was improved when using AHR as an additional guide to long-term treatment of asthma.

Further reading

- Anderson SD (2010). Indirect challenge tests: airway hyperresponsiveness in asthma: its measurement and clinical significance. *Chest*; 138: Suppl 2, 25S–30S.
- Carlsen KH, *et al.* (1998). Cold air inhalation and exercise-induced bronchoconstriction in relationship to methacholine bronchial responsiveness: different patterns in asthmatic children and children with other chronic lung disease. *Respir Med*; 92: 308–315.
- Coates AL, *et al.* (2017). ERS technical standard on bronchial provocation testing: general considerations and performance of methacholine challenge tests. *Eur Respir J*; 49: 1601526.
- Crapo RO, *et al.* (2000). Guidelines for methacholine and exercise challenge testing – 1999. *Am J Respir Crit Care Med*; 161: 309–329.
- Diamant Z, *et al.* (2013). Inhaled allergen bronchoprovocation tests. *J Allergy Clin Immunol*; 132: 1045–1055.
- Hallstrand TS, *et al.* (2018). ERS technical standard on bronchial challenge testing: pathophysiology and methodology of indirect airway challenge testing. *Eur Respir J*; 52: 1801033.
- Perpiná M, *et al.* (1993). Diagnostic value of the bronchial provocation test with methacholine in asthma. *Chest*; 104: 149–154.
- Sont JK, *et al.* (1999). Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long term treatment. *Am J Respir Crit Care Med*; 159: 1043–1051.
- Sterk PJ, *et al.* (1993). Standardized challenge testing with pharmacological, physiological and sensitizing stimuli in adults. *Eur Respir J*; 6: 53–83.
- Sterk PJ (1996). Bronchial hyperresponsiveness: definitions and terminology. *Pediatr Allergy Immunol*; 7: Suppl. 9, 7–9.

Static and dynamic lung volumes

Riccardo Pellegrino, Andrea Antonelli and Frans de Jongh

Ventilation is constrained by the mechanical properties of the airways, lung and chest wall. The latter two determine the volume at which the movement of gas is accomplished at rest and in daily activities such as exercise, phonation, laughing, changes in body posture, *etc*. However, when cardiopulmonary disease is present, lung volumes may also be modified as a result of dynamic mechanisms within the airways and changes in breathing pattern, in addition to static changes in lung and chest wall properties.

Static lung volumes are defined as lung volumes that are not affected by the rate at which air is in- and expired. Dynamic lung volumes are those that do depend on the rate at which air flows in or out of the lungs. In clinical practice, the most used dynamic lung volumes are the forced vital capacity (FVC) and the forced expiratory volume in 1 s (FEV_1). In addition, the maximal voluntary ventilation (MVV), being the amount of air that can maximally be in- and exhaled in 1 min, is called a dynamic lung volume. Due to the invasiveness of the MVV measurement for the patient and the limited clinical value, MVV measurements are nowadays seldom performed and thereby often not listed as a dynamic lung volume. The most used static lung volumes are the residual volume (RV), the functional residual capacity (FRC) and the total lung capacity (TLC).

Determinants of lung volumes in health and disease

Tidal volume (V_T) is the volume of gas inspired during each breath (figure 1) necessary to preserve gas exchange. In healthy subjects, inspiration is switched off by neural reflexes, whereas expiration is terminated near the relaxation volume as a result of static or dynamic mechanisms (see FRC later). Except during exercise, when a lack of increase in V_T with ventilation is a functional marker of ventilatory limitation, and

Key points

Measurement of lung volumes in clinical practice has been proven to be important to assist in:

- Diagnosis of pulmonary defects
- Prognosis of COPD and interstitial lung diseases
- Evaluation of the bronchomotor response to constrictor and dilator agents as well as to physical exercise

New worldwide reference values for dynamic lung volumes have been published and those of static lung volumes will follow.

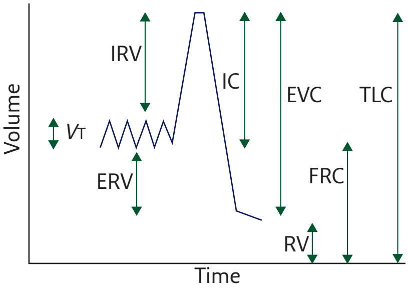


Figure 1. Lung volume plotted versus *time.*

perhaps in patients undergoing assisted ventilation, V_T has little usefulness in clinical practice due to its high natural variability.

TLC is the volume of gas contained in the lungs after a deep breath. It is determined by the maximum force exerted by the inspiratory muscles to balance lung and chest wall elastic recoils (figures 1 and 2).

Under healthy conditions, TLC tends to remain fairly stable with age, presumably because the natural decrease in the force of the inspiratory muscles and/or the increase in chest wall stiffness are balanced by the progressive loss of lung elastic recoil. Sports like swimming are associated with an increase in TLC as a result of an increase in inspiratory muscle force.

In contrast, TLC tends to increase in emphysema, and sometimes in chronic bronchitis and severe asthma. Though the decrease in lung elastic recoil is presumably the most important mechanism of the increase in TLC under these conditions, an increased force of the inspiratory muscles and chest wall remodelling may also play a role. Surprisingly, for the same level of airflow obstruction, TLC tends to increase during spontaneous long-lasting but not acutely induced bronchospasm. This is presumably because of the different time course necessary to produce airflow obstruction and hyperinflation. That this may be so was shown by a study documenting that when a resistive valve was implanted in a dog trachea, it took time for TLC to increase. Thus,

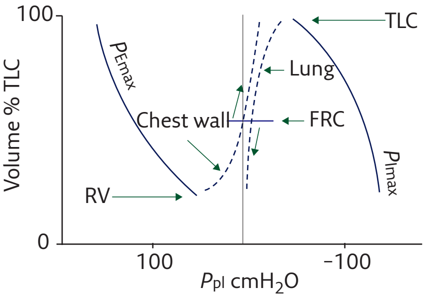


Figure 2. Quasistatic pressure–volume curves of the chest wall and the lung (dashed lines) related to pleural pressure (P_{pl}) generated during maximum inspiratory and expiratory static efforts (P_{Imax} and P_{Emax}, respectively; continuous lines). Volume is expressed as a percentage of TLC. TLC is the volume at which P_{Imax} equals the inward elastic recoils of both lung and chest wall. RV is the volume at which P_{Emax} overcomes the outward elastic recoil of the chest wall. FRC is the volume at which inward lung recoil equals outward chest wall recoil (arrows with opposite direction).

it is possible that breathing at high lung volumes for long periods of time as a result of severe chronic airflow obstruction may also contribute to the increase in TLC.

TLC decreases in all conditions characterised by an increase in lung elastic recoil (*e.g.* pulmonary fibrosis and cardiac failure), chest wall stiffness (*e.g.* neuromuscular diseases, obesity, ascites and pregnancy) or thoracic space competition (*e.g.* pleural effusions and pneumothorax).

Measuring TLC is of great importance in clinical practice, as it allows the identification of restrictive pulmonary defects. In addition, TLC is useful in the evaluation of an emphysematous patient as a candidate for lung volume reduction coils or valves, or for follow-up of interstitial lung diseases.

Residual volume (RV) is the volume of gas that remains in the lungs after a complete expiration. In young healthy individuals, RV is, for the most part, determined by the balance between the force of the expiratory muscles and the outward recoil of the chest wall (figures 1 and 2). In the elderly, it increases as a result of airway closure or reduced lung elastic recoil.

In restrictive diseases, RV decreases in proportion to the increase in lung elastic or chest wall recoils and/or loss of lung parenchyma. In obstructive pulmonary diseases, RV is higher than predicted because of premature airway closure, loss of lung elastic recoil and stiffness of the chest wall. Additional mechanisms may dynamically contribute to the elevation of RV in obstructive lung diseases. For instance, in patients with acutely induced or chronic airflow obstruction, RV achieved after a forced expiration is always higher than after a slow expiration. This is mainly because of two mechanisms. First, during forced expiration in airflow obstruction, expiratory flow limitation (EFL) occurs soon after initiation of the manoeuvre, especially within the airways that are already narrowed. In contrast, during a slow expiration, pleural pressure will not exceed the critical pressure necessary to generate maximal flow, thus allowing EFL to occur late in expiration and at a lower lung volume. Secondly, some airways could close near TLC early in expiration as a result of disease, thus preventing the subtending alveolar units from emptying and contributing to the increase in RV.

In addition, the effects of volume history of the manoeuvre preceding the expiration may affect RV. For instance, in healthy subjects or mild-to-moderate asthmatics exposed to a bronchoconstrictor agent, a manoeuvre initiated from TLC will generate greater flow and lower RV than a manoeuvre initiated from end-tidal inspiration. The opposite occurs in chronic airflow obstruction. This suggests that RV is also modulated through the changes in airway calibre caused by large lung inflations. How the deep inspiration manoeuvre affects lung and airway mechanics is still a matter of debate. When a deep breath is taken, the inflating stimulus is transmitted to the lung as well as the airways through the elastic network of lung parenchyma. The effects of volume history on airway size depend on the mechanical characteristics of the lung parenchyma and airways. Both tissues may lose energy or pressure and deform with stretching, a phenomenon called hysteresis. Since lung elastic recoil and transmural pressure are the forces that determine airway size, any change relative to one of these will necessarily entail a change in flow and RV.

Vital capacity (VC) is the difference between TLC and RV. Because RV is dependent on volume and flow histories in addition to airway, parenchyma and/or chest wall components of the diseases, VC will depend on the type of respiratory manoeuvre from which it is taken and the underlying disease. In general, the largest VC is that obtained during a full inflation from RV (achieved after a slow expiration from end-tidal inspiration) to TLC (inspiratory vital capacity (IVC)), followed by the slow expiratory vital capacity (EVC) from TLC to RV and the VC measured during a forced expiratory manoeuvre (FVC). A decrease in VC does not allow differentiation between restriction and obstruction, as it may be due to a decrease in TLC or an increase in RV, or both.

The reason that the IVC is normally the highest is due to the fact that during inspiration, the diaphragm is lowered and the ribcage is lifted, thereby creating a high negative intrapleural pressure around the lungs. This high negative pressure 'stents' the bronchi. As soon as the air flows into the lungs, the pressure inside the bronchi becomes lower (by Bernoulli's law, which states that a higher airflow in a tube will lead to a lower pressure in that tube). One can see this effect by, for instance, blowing between two paper sheets close to each other and seeing that those sheets tend to move nearer to each other, finally leading to a collapse, after which the airflow ceases and the sheets will re-open. This is the same as during an IVC manoeuvre, where the high negative pressure opens up the airways, counteracted by the collapsing force of the high inspiratory flow reached during such a fast inspiratory manoeuvre. It can be seen from the round part from the inspiratory forced flow–volume curve that the airways remain open during an IVC manoeuvre. A prerequisite is that one should go very slowly from FRC to RV to minimise the collapsing force due to airflow.

During forced expiration, the intrapleural pressure will become highly positive, already trying to collapse the bronchi. As soon as the expiratory flow starts and the pressure inside the bronchi becomes lower due to the high flow, the collapsing force is enhanced, leading to the typically pointed triangular shape of the expiratory part of the flow–volume curve. Therefore, the IVC is normally always equal to or higher than the FVC but many simple spirometry devices, especially those used in primary care, cannot measure the IVC, and the FVC became the world standard (and was abbreviated as VC). A slow manoeuvre from TLC to RV, also called the expiratory vital capacity (EVC), will lead to a lower airflow in the bronchi and thereby less pressure reduction, but will still be lower than the IVC.

In clinical practice, VC is of central importance for the diagnosis of obstructive pulmonary defects. The higher the degree of airway obstruction, the more severe the asthma or COPD, and the larger the difference between IVC and FVC becomes.

When one calculates the Tiffeneau index, one should divide the FEV_1 by the IVC. Mostly, the FEV_1 is divided by the FVC but this is officially called the forced expiratory ratio (FER). For a patient with a severe airway obstruction, the FER can become significantly higher than the Tiffeneau index (if the IVC is much larger than the FVC). Severity of airway obstruction is, however, graded by the FEV_1 itself and this is unaffected.

FRC is the volume of gas remaining in the lungs at the end of a tidal expiration performed in a seated or upright position (figure 1). Its mechanical determinants are the inward elastic recoil of the lung and the opposing outward recoil of the chest wall (figure 2). In the supine position, the abdominal content is displaced towards the chest cavity, thus reducing FRC. In addition, during speech, singing, laughing or exercise, FRC tends to decrease to favour these activities.

In obstructive pulmonary diseases, FRC tends to increase for several reasons. For instance, an increase in breathing frequency or in time constant of the respiratory system, as a result of either an increase in airflow resistance or an increase in lung compliance, will lead to an expiratory time that is relatively too short to allow the respiratory system to empty fully. Presumably, the occurrence of EFL during tidal expiration may also contribute to an increase in FRC to a lung volume where EFL is minimal. Under these circumstances, the dynamic compression of the airways downstream from the flow limiting segment may evoke neural reflexes that prematurely activate the inspiratory muscles to avoid breathing for too long a time under EFL conditions. On the one hand, the increase in FRC in airflow obstruction is beneficial as it allows breathing at a volume where the airways are larger, thus decreasing the resistive work of breathing. On the other hand, however, breathing at high lung volume is associated with an increase in the elastic work of breathing and causes dyspnoea.

A decrease in FRC occurs in restrictive respiratory diseases due to an increase in lung elastic recoil (*e.g.* in pulmonary fibrosis, atelectasis, lung resection, alveolar liquid filling and cardiac diseases) or in chest wall elastance (*e.g.* in chest wall and pleural diseases, respiratory muscle paralysis and obesity). This is important, as reduced FRC is associated with hypoxaemia and, in obesity, with increased airway responsiveness. The higher airway resistance and lower compliance of the respiratory system at lower lung volumes will increase work of breathing, and might lead to dyspnoea.

Inspiratory capacity (IC) is the volume difference between TLC and FRC. In pulmonary diseases, it tends to decrease as a result of an increase in FRC (obstructive conditions) or a decrease in TLC (restrictive diseases), or both. In clinical practice, changes in IC with acute interventions on airway calibre, such as bronchoprovocation or reversibility tests, or during exercise, reflect mirror-like changes in FRC, assuming that TLC remains unmodified.

IC has no role in the diagnosis of ventilatory defects but a reduced IC due to hyperinflation leads to dyspnoea. Hyperinflation is diagnosed if FRC and/or RV are elevated. If aerosol medication opens the peripheral airways, one might even see an increase in VC without an increase in FEV_1 (which more reflects the collapsibility of the central/larger airways). Sometimes, this is called ‘a volume response’ instead of a flow response. Nowadays, some body plethysmographs can measure the airway resistance and intrathoracic gas volume (which equals FRC) in a connected manoeuvre, thereby offering the possibility of giving a resistance–volume loop as the outcome. After a bronchodilator, the airways might open, thereby lowering the airway resistance and/or lowering the hyperinflation. Of course, this occurs mostly in severe COPD or asthma, in which the resistance volume after medication can objectively quantify the beneficial effect of the bronchodilator. Often, the FEV_1 will also be increased but this is not necessarily the case. Patients do, however, feel benefit from the lower airway resistance and/or decreased hyperinflation, and might report less dyspnoea, even in cases where FEV_1 remains unchanged.

Expiratory reserve volume (ERV) and inspiratory reserve volume (IRV) allow V_T to expand when necessary (figure 1). Though of little interest at rest, they play a critical role during exercise. For instance, in healthy subjects, the increase in V_T with exercise is achieved at the expense of a decrease in end-expiratory lung volume (EELV) and an increase in end-inspiratory lung volume (EILV). In contrast, in airflow obstruction, the increase in V_T is limited by the premature and sustained increase in EELV that may eventually contribute to causing dyspnoea together with the increase in EILV near TLC.

Measurements of lung volumes in clinical practice: technical aspects

VC, V_T, IC, EILV and EELV can be measured by simple spirometry. In contrast, TLC, RV and FRC need to be measured with the following special techniques.

Gas dilution techniques (nitrogen washout and helium dilution) are based on the principle of the conservation of mass; that is, the amount of gas resident in the lungs at the beginning of the test can be calculated as the product of concentration and volume of eliminated nitrogen or diluted helium. Both methods yield measurements of lung volumes that reflect open airways only. In severely obstructed patients, an underestimation of the true lung volume may be a result of some regions with long time constants.

Body plethysmography allows rapid and reproducible measurements of absolute lung volumes. The test is based on Boyle's law, in that lung volume can be calculated from the relationship between changes in mouth pressure (assumed to be equal to alveolar pressure) and box pressure (constant-volume plethysmography) or volume (constant-pressure plethysmography) during gentle panting manoeuvres against a closed shutter. In contrast to gas dilution techniques, plethysmography measures the whole intrathoracic gas, thus including nonventilated and/or poorly ventilated lung regions. This method may overestimate lung volumes in cases of severe airflow obstruction if the panting frequency is >1 Hz.

Normal values for static and dynamic lung volumes are necessary to see if a patient's lung function is within the normal range. In Europe, one of the most used lung function normal value sets was that of the European Community of Coal and Steel, which in 1993 was formed to see if the lung function of coal mine workers was affected by their work. Mean values for almost all dynamic and static lung volumes were given with a standard deviation of those volumes. In 2012, the Global Lung Function Initiative published new reference values for dynamic lung volumes for 3–95-year-old healthy persons based on numerous data for most ethnicities. Standard deviation of parameters like FEV_1 and FVC were shown to be strongly dependent on (amongst other factors) age. It is thereby misleading to take a fixed percentage of predicted as lower limit of normal (*e.g.* 70% or 80% of a certain normal value). One should instead work with z-scores, which are simply the number of standard deviations a value lies from its mean. Worldwide multiethnic reference values for a wide age range for static lung volumes are expected in 2019.

Conclusion

Measuring lung volumes is now an integral part of lung function assessment. In addition to assisting in the diagnosis of ventilatory defects, it helps explain the presence of respiratory symptoms and hypoxia in cardiopulmonary diseases, has clinical prognostic implications in both obstructive and restrictive diseases, and plays an integral role in the functional evaluation for lung volume reduction in emphysema.

Further reading

- Agostoni E, *et al.* (1986). Static behaviour of the respiratory system. *In:* Macklem PT, *et al.*, eds. Handbook of Physiology. The Respiratory System. Mechanics of breathing. Section 3, Vol. III, part 1. Bethesda, American Physiological Society; pp. 113–130.
- Brusasco V, *et al.* (1997). Vital capacities during acute and chronic bronchoconstriction. Dependence of flow and volume histories. *Eur Respir J*; 10: 1316–1320.
- Casanova C, *et al.* (2005). Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 171: 591–597.
- King TE Jr, *et al.* (2001). Predicting survival in idiopathic pulmonary fibrosis. Scoring system and survival model. *Am J Respir Crit Care Med*; 164: 1171–1181.

- O'Donnell DE, *et al.* (2007). Pathophysiology of dyspnea in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*; 4: 145–168.
- Olive JT, *et al.* (1972). Maximal expiratory flow and total respiratory resistance during induced bronchoconstriction in asthmatic subjects. *Am Rev Respir Dis*; 106: 366–376.
- Pellegrino R, *et al.* (1979). Expiratory flow limitation and regulation of end-expiratory lung volume during exercise. *J Appl Physiol*; 74: 2552–2558.
- Pellegrino R, *et al.* (1996). Lung mechanics during induced bronchoconstriction. *J Appl Physiol*; 81: 964–975.
- Pellegrino R, *et al.* (2005). Interpretative strategies for lung function tests. Official statement of the American Thoracic Society and the European Respiratory Society. *Eur Respir J*; 26: 948–968.
- Pride NB, *et al.* (1986). Lung mechanics in disease. In: Macklem PT, Mead J, eds. Handbook of Physiology. The Respiratory System. Mechanics of breathing. Section 3, Vol. III, part 2. Bethesda, American Physiological Society; pp. 659–692.
- Torchio R, *et al.* (2009). Mechanical effects of obesity on airway responsiveness in otherwise healthy humans. *J Appl Physiol*; 107: 408–416.
- Fragoso CAV, *et al.* (2017). Spirometry, static lung volumes, and diffusing capacity. *Respir Care*; 62: 1137–1147.
- Quanjer PH, *et al.* (2012). Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J*; 40: 1324–1343.

Assessment for anaesthesia/surgery

Macé M. Schuurmans, Carolin Steinack and Markus Solèr

Pre-operative assessment is important in order to identify patients at risk for peri- and post-operative pulmonary morbidity and mortality, to determine possible pre- and peri-operative interventions to reduce that risk and to identify patients where the risk may be prohibitive.

A careful history and physical examination are the most important tools for assessment of risk for post-operative pulmonary complications. Post-operative pneumonia is the most frequent and potentially dangerous pulmonary complication and its incidence is closely related to pre-existing sputum hypersecretion and productive cough. Patients with known pulmonary diseases and patients with symptoms suggesting occult underlying lung disease (exercise intolerance, unexplained dyspnoea and cough), therefore, need to be assessed and peri-operative treatment adjusted accordingly.

Reduced functional and physical status before surgery correlates with increased peri-operative complications, especially for the elderly. Pre-habilitation to improve general physical status by endurance and muscle exercises before surgery is as important as post-operative rehabilitation to reduce pulmonary complications. If a delay of an elective surgical intervention is reasonable, pre-habilitation with training sessions three times per week should be started 6 weeks before surgery.

Many risk factors for increased post-operative pulmonary complications need to be considered, in particular those listed in table 1. The American Society of Anesthesiologists (ASA) classification of pre-operative risk is also useful for determination of general health status (table 2).

Key points

- A careful history and physical examination are necessary to assess the risk of post-operative pulmonary complications, according to widely accepted risk factors.
- Pulmonary function testing is not routine, except in the case of evaluation for lung resection.
- A number of strategies are available to reduce the risk of complications by recognising and addressing known risk factors. Pre-habilitation is one option to address a number of risk factors and should be performed if a delay in the surgery is reasonable.

Table 1. Factors indicating increased risk for pulmonary complications

Surgery-specific risk factors

- Upper abdominal procedures
- Aortic, thoracic, and head and neck surgery, including neurosurgery
- Surgery lasting >3 h
- Emergency procedures

Patient-related risk factors

- Definite risk factors
  - COPD
  - CHF
  - Diminished general health status, ASA class ≥2 (table 2)
  - Malnutrition (serum albumin <35 mg·L^{-1})
  - Use of pancuronium as a neuromuscular blocker
  - Opioid use
  - Obesity
  - Diabetes mellitus
  - History of difficult airway
- Probable risk factors
  - Current upper respiratory tract infection
  - OSA
  - General anaesthesia (when compared with spinal or epidural anaesthesia)
  - Pulmonary hypertension
  - Abnormal chest radiograph
  - Cigarette use within previous 8 weeks
  - Alcohol dependence

Table 2. ASA classification of pre-operative risk

ASA class	Systemic disturbance	PPC %	Mortality %
1	Healthy patient with no disease outside of the surgical process	1.2	<0.03
2	Mild-to-moderate systemic disease caused by the surgical condition or by other pathological processes, medically well controlled	5.4	0.2
3	Severe disease process that limits activity but is not incapacitating	11.4	1.2
4	Severe incapacitating disease process that is constant threat to life	10.9	8
5	Moribund patient not expected to survive 24 h with or without an operation	NA	34
E	Suffix to indicate emergency surgery for any class	Increased	Increased

PPC: post-operative pulmonary complications; NA: not applicable. Reproduced and modified from Koegelenberg *et al.* (2008) with permission.

Table 3. STOP-BANG screening tool for OSA

Snoring	Do you snore loudly (loud enough to be heard through closed doors, or your bed-partner elbows you for snoring at night)?
Tired	Do you often feel tired, fatigued or sleepy during the daytime (such as falling asleep during driving or talking to someone)?
Observed	Has anyone observed you stop breathing or choking/gasping during your sleep?
Pressure	Do you have or are you being treated for high blood pressure?
BMI	Is your BMI >35 $kg \cdot m^{-2}$?
Age	Are you older than 50 years?
Neck size	Is your neck size large? (measured around the Adam's apple) For males, is your shirt collar 17 inches/43 cm or larger? For females, is your shirt collar 16 inches/41 cm or larger?
Gender	Male?

Scoring algorithm: a 'yes' or 'no' answer is given to each question; the number of 'yes' answers defines the risk. Reproduced and modified from www.stopbang.ca with permission from the University Health Network (UHN, Toronto, ON, Canada). We acknowledge Frances Chung and UHN as the owner of this tool. This tool is displayed for educational purposes and any use of the tool requires a licence from UHN.

Detection of previously unrecognised OSA by a screening tool such as the STOP-BANG questionnaire (table 3) has been recommended. In surgical patients, a greater STOP-BANG score is associated with a greater probability of moderate-to-severe OSA.

It is noteworthy that pulmonary function tests are not part of routine pre-operative assessment unless patients are being evaluated for lung resection (see later). Pulmonary function tests and further standard diagnostic work-up should, however, be performed in patients with unexplained dyspnoea or exercise intolerance, and if clinical evaluation cannot determine whether airflow obstruction has been optimally reduced in patients with previously diagnosed COPD or asthma. Well-controlled asthma (free of wheezing, and peak flows >80% of the predicted value or the patient's personal best) has been shown not to carry any added risk. Age and blood gases have no definitive role in the risk assessment when confounding issues such as comorbidities have been considered.

Cardiac evaluation

History, physical examination and resting ECG are used for the initial estimate of the peri-operative cardiac risk. Only unexplained dyspnoea or other clinical signs of cardiac failure require an echocardiogram in addition to the ECG. The inability to climb two flights of stairs or run a short distance indicates poor cardiopulmonary functional capacity and is associated with an increased incidence of post-operative cardiac events. The definitive assessment of cardiac risk should respect current guidelines for cardiologists. The Revised Cardiac Risk Index is one established option to identify patients at high risk (table 4).

Patients with high risk (a surgery-specific risk factor plus one or more definite risk factors) have been shown to benefit from interventions to reduce pulmonary complications, as listed in table 5.

Table 4. The Revised Cardiac Risk Index

1	History of ischaemic heart disease
2	History of congestive heart failure
3	History of cerebrovascular disease (stroke or transient ischaemic attack)
4	History of diabetes requiring pre-operative insulin use
5	Chronic kidney disease (creatinine $>2\ \text{mg}\cdot\text{dL}^{-1}$ or $>177\ \mu\text{mol}\cdot\text{L}^{-1}$)
6	Undergoing suprainguinal vascular, intraperitoneal or intrathoracic surgery

Risk for cardiac death at 30 days, nonfatal myocardial infarction and nonfatal cardiac arrest after noncardiac surgery: 0 predictors = 3.9%, 1 predictor = 6%, 2 predictors = 10.1%, ≥3 predictors = 15%. Reproduced and modified from Duceppe *et al*. (2017) with permission.

Table 5. Interventions effective in reducing risk for complications

Pre-operative interventions

- Smoking cessation for at least 8 weeks
- Inhaled anticholinergic agent for patients with clinically significant COPD
- Inhaled β-agonists for symptomatic COPD and asthma patients
- Pre-operative systemic glucocorticoids ($0.5\ \text{mg}\cdot\text{kg}^{-1}$ body weight for 5 days) for COPD and asthma patients who are not optimised on inhaled treatment
- Delay elective surgery if respiratory infection present
- Antibiotics for patients with purulent sputum or change in sputum character
- Pre-habilitation
- Inspiratory muscle training
- Psychological care
- Peri-operative medication influencing cardiovascular complications and mortality:
  - Continuing angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is reasonable; if they are paused pre-operatively, resumption should occur post-operatively as soon as possible
  - Continuing beta-blockers is beneficial in high-risk patients receiving high-risk procedures (*i.e.* having three or all of the following: serum creatinine level $>2\ \text{mg}\cdot\text{dL}^{-1}$, coronary artery disease, diabetes, surgery in a major body cavity (abdomen or chest)); in other patients, newly introducing such treatment may be harmful
  - Starting a statin before surgery and continuing it peri-operatively seems appropriate in patients at high risk

Intra-operative interventions

- Choose alternative procedure lasting <3 h if possible (video-assisted thoracoscopic and laparoscopic procedures have approximately one tenth of the pulmonary complication rates of open procedures)
- Minimise duration of anaesthesia
- Regional anaesthesia (nerve block) in very high-risk patients
- Avoid pancuronium

Post-operative interventions

- Deep-breathing exercises or incentive spirometry
- Early mobilisation
- Epidural analgesia instead of parenteral opioids
- Selective use of nasogastric tube if post-operative nausea or vomiting, inability to tolerate oral intake, or symptomatic abdominal distension

Pulmonary resection

Pulmonary resection is a high-risk procedure with a mortality of 2–3% for lobectomy and 4–6% for pneumonectomy in experienced centres. Clinical evaluation should focus on respiratory and cardiovascular pathology. Air flow limitation should be optimised before further evaluation, and cardiac disease identified and managed either medically or surgically. Initial pulmonary function evaluation should include at least FEV1, FVC and *T*LCO. Values >80% predicted for FEV1 and *T*LCO are associated with an uncomplicated surgical course for resection up to a pneumonectomy. All other candidates should undergo a formal exercise test. Patients with a maximal oxygen uptake ($V'_{O_2\max}$) >20 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (or >75% pred) tolerate pulmonary resection up to a pneumonectomy, and values >15 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (or >60% pred) are sufficient for lobectomy. Values <10 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ are predictive of major post-operative complications and disability.

Further evaluation according to a validated algorithm (figure 1) necessitates the estimation of the relative contribution of the tissue earmarked for resection by means of the predicted post-operative (ppo) values of FEV1, *T*LCO and $V'_{O_2\max}$ ('split function'). The ppo values of these parameters can be calculated as follows: ppo values=pre-operative values×(1–fractional contribution of the tissue earmarked for resection). There are three acceptable ways of estimating the relative functional contribution or split lung function: 1) anatomical calculation, 2) quantitative CT, and 3) split perfusion scanning.

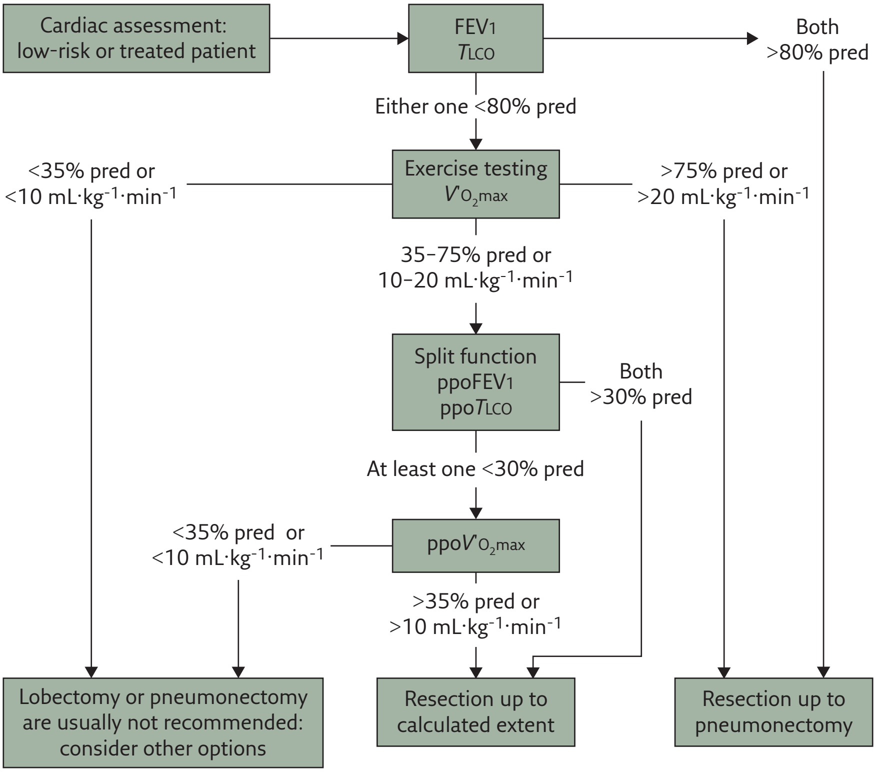

Cardiac assessment: low-risk or treated patient
FEV1 TLCO
Both >80% pred
Either one <80% pred
Exercise testing V'O2max
<35% pred or <10 mL·kg-1·min-1
>75% pred or >20 mL·kg-1·min-1
35–75% pred or 10–20 mL·kg-1·min-1
Split function ppoFEV1 ppoTLCO
Both >30% pred
At least one <30% pred
ppoV'O2max
<35% pred or <10 mL·kg-1·min-1
>35% pred or >10 mL·kg-1·min-1
Lobectomy or pneumonectomy are usually not recommended: consider other options
Resection up to calculated extent
Resection up to pneumonectomy

Figure 1. Algorithm for assessment of cardiopulmonary reserve before lung resection in lung cancer patients. Reproduced and modified from Brunelli et al. *(2009) with permission.*

Anatomical calculations are by far the simplest: the number of patent (or functional) segments that are due for resection is subtracted from the total number of segments (19) and this value is divided by 19 to give a fraction. The ppoFEV1 is thus estimated as follows: ppoFEV1=pre-operative FEV1×((19–patent segments removed)/19). Anatomical calculations have been shown to overestimate the functional loss so that patients who are deemed operable by anatomical calculations will generally not require radiological calculations.

Calculated ppo values based on lung perfusion scans (with technetium-99m-labelled albumin-macroaggregates) have been shown to correlate best with actual post-operative values. Densitometric calculations on the basis of CT are marginally less accurate than perfusion scans. The advantage of this method is the availability of the information, as most lung resection candidates invariably have a pre-operative chest CT and modern software simplifies the three-dimensional reconstruction for the calculation of the relative volume of lung to be resected.

Simple stair climbing as a low-cost alternative to assess exercise capacity and operative risk is increasingly being used. A number of recent studies have shown that the ability to climb an elevation >22 m is correlated with a favourable surgical outcome for lung resection surgery. Patients unable to reach this elevation then require more sophisticated ergometric evaluation. Adding a time component to the evaluation of the stair-climbing test appears to quantify the overall exercise performance more precisely: data from one study additionally assessing speed of ascent during stair climbing showed that patients reaching or passing the 20-m elevation mark within 80 s all had formal exercise tests permitting resection up to the extent of a pneumonectomy. For early-stage (stage I) lung cancer treatment, climbing to 18-m elevation is associated with a more favourable outcome than for those who do not reach this cut-off.

Lung volume reduction surgery for end-stage emphysema has partly redefined the limits of lung resection. Traditional cut-off limits are too prohibitive for these patients, as resection of largely nonfunctional emphysematous tissue leads to improved lung mechanics, improving the overall outcome. The latter is also partly true for moderate-to-severe COPD patients undergoing surgery for lung cancer. Patients with either ppoFEV1 or ppo*T*LCO <40% pred, or both parameters between 30% and 40% pred, can undergo extensive resections such as lobectomy or even pneumonectomy with reasonable safety (mortality of 13.5%) if they have a ppo$V'_{O_2\mathrm{max}}$ of >10 mL·kg^{-1}·min^{-1}. Survival following this strategy appears to be superior to that for the nonsurgical strategy.

Further reading

- Bernasconi M, *et al.* (2012). Speed of ascent during stair climbing identifies operable lung resection candidates. *Respiration*; 84: 117–122.
- Bolliger CT, *et al.* (2002). Prediction of functional reserves after lung resection: comparison between quantitative computed tomography, scintigraphy, and anatomy. *Respiration*; 69: 482–489.
- Brunelli A, *et al.* (2009). ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J*; 34: 17–41.
- Brunelli A, *et al.* (2014). Preoperative maximum oxygen consumption is associated with prognosis after pulmonary resection in stage I non-small cell lung cancer. *Ann Thorac Surg*; 98: 238–242.

- Chung F, *et al.* (2016). Society of Anesthesia and Sleep Medicine guideline on preoperative screening and assessment of adult patients with obstructive sleep apnea. *Anesth Analg*; 123: 452–473.
- Cohn SL, *et al.* (2016). Update in perioperative cardiac medicine. *Cleve Clin J Med*; 83: 723–730.
- Duceppe E, *et al.* (2017). Canadian Cardiovascular Society guidelines on perioperative cardiac risk assessment and management for patients who undergo noncardiac surgery. *Can J Cardiol*; 33: 17–32.
- Fleisher LA, *et al.* (2014). 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation*; 130: e278–e333.
- Koegelenberg CFN, *et al.* (2008). Preoperative pulmonary evaluation. *In*: Albert RK *et al.*, eds. Clinical Respiratory Medicine. 3rd Edn. Philadelphia, Elsevier; pp. 275–283.
- Puente-Maestú L, *et al.* (2011). Early and long-term validation of an algorithm assessing fitness for surgery in patients with postoperative FEV1 and diffusing capacity of the lung for carbon monoxide <40%. *Chest*; 139: 1430–1438.
- Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery, *et al.* (2009). Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. *Eur Heart J*; 30: 2769–2812.
- von Groote-Bidlingmaier F, *et al.* (2011). Functional evaluation before lung resection. *Clin Chest Med*; 32: 773–782.

Dyspnoea

Pierantonio Laveneziana

Dyspnoea is the major reason for referral for pharmacological treatment and respiratory rehabilitation programmes in patients with COPD. Dyspnoea is a subjective experience of breathing difficulty that consists of qualitatively distinct sensations that vary in intensity. This definition underlines the importance of the different qualities (cluster descriptors) covered by the term dyspnoea, the involvement of integration of multiple sources of neural information about breathing and the physiological consequences. More specifically, it has been postulated that dyspnoea arises when there is a conscious awareness of a mismatch between what the brain expects and what it receives in terms of afferent information from the lungs, airways and receptors in the tendons and muscles of the chest wall (figure 1 and table 1). The relevance of assessing and documenting dyspnoea also stems from the following observations.

1) Up to a quarter of the general population and half of severely ill patients are affected by this symptom.
2) Dyspnoea appears to be an important predictor of quality of life, exercise tolerance and mortality in various conditions; in patients with COPD, dyspnoea has been found to be a better predictor of mortality than FEV_1; in patients with heart disease referred for clinical exercise testing, it is a better predictor of mortality than angina.

Key points

- Dyspnoea is a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity.
- The mechanisms of dyspnoea are complex and multifactorial: there is no unique central or peripheral source of this symptom.
- The sense of heightened inspiratory effort is an integral component of exertional dyspnoea and is pervasive across health and disease.
- The neuroventilatory dissociation (NVD) theory of dyspnoea states that the symptom arises when there is a disparity between the central reflex drive (efferent discharge) and the simultaneous afferent feedback from a multitude of peripheral sensory receptors throughout the respiratory system. The feedback system provides information about the extent and appropriateness of the mechanical response to central drive.
- Despite the diversity of causes, the similarity of described experiences of dyspnoea suggests common underlying mechanisms.

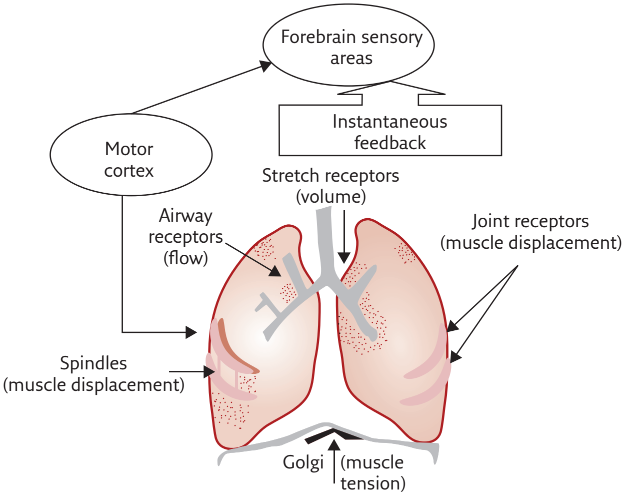

Forebrain sensory areas
Instantaneous feedback
Motor cortex
Stretch receptors (volume)
Airway receptors (flow)
Joint receptors (muscle displacement)
Spindles (muscle displacement)
Golgi
(muscle tension)

Figure 1. Schematic representation of the neurophysiological underpinnings of perceived dyspnoea during exercise in healthy humans. During a voluntary increase in ventilation, the motor cortex increases the outgoing motor signal to the respiratory muscles and conveys a copy (central corollary discharge) through cortical interneurons to the sensory/association cortex, which is informed of the increased motor drive to increase ventilation. Volitional respiratory effort in healthy subjects is harmoniously matched with the appropriate increase in flow or volume displacement via *concurrent afferent proprioceptive information transmitted* via *vagal, glossopharyngeal, spinal and phrenic nerves. This information is conveyed to the medulla and central cortex, where it is integrated. The result is a harmonious neuromechanical coupling with avoidance of respiratory discomfort or distress. Reproduced and modified from Scano* et al. *(2010)* Respir Med*; 104: 925–933, with permission from the publisher.*

Table 1. Putative neurophysiological basis of exertional dyspnoea

Central (corollary discharge)	↑ motor drive (inspiratory effort): cortical
	↑ reflex drive (chemical, neural): medullary
Peripheral (afferent activity)	Airway/lung receptors (pulmonary stretch receptors, C-fibres, J-receptors)
	Ventilatory muscle receptors (muscle spindles, Golgi tendon organs, joint receptors, type III and IV mechano- and metaboreceptors in the diaphragm and chest wall muscles)
	Peripheral chemoreceptors
	Locomotor muscles receptors (type III and IV afferents)

The most important receptors (afferences) and efferences to respiratory and locomotor muscles involved in the putative pathogenesis of exertional dyspnoea in cardiopulmonary disease. Please see the main text for more details.

3) Dyspnoea is associated with decreased functional status and worse psychological health in older individuals living at home.
4) It is a factor in the low adherence to exercise training programmes in sedentary adults and in patients with COPD.
5) The effective management of exertional dyspnoea remains a major challenge for caregivers, and modern treatment strategies that are based on attempts to reverse the underlying chronic condition are only partially successful.

Evaluation of dyspnoea during physical tasks

Exertional dyspnoea can be easily defined as ‘the perception of respiratory discomfort that occurs for an activity level that does not normally lead to breathing difficulty’ (Killian *et al.*, 1995). It follows that the intensity of dyspnoea can be determined by assessing the activity level required to produce dyspnoea (*i.e.* dyspnoea at rest is more severe than dyspnoea only when climbing stairs). The Medical Research Council (MRC) dyspnoea scale can be used for this purpose (table 2), as well as other scales such as the Baseline Dyspnoea Index. Dyspnoea can also be evaluated during a physical task, such as cardiopulmonary exercise testing (CPET). For this purpose, the 10-point Borg scale can be used (table 2). In the Borg scale, the end-points are anchored such that zero represents ‘no breathlessness at all’ and 10 is ‘the most severe breathlessness that

Table 2. The MRC dyspnoea scale and the Borg scale

Grade	Description
MRC dyspnoea scale	
1	Not troubled by breathlessness except with strenuous exercise
2	Troubled by shortness of breath when hurrying on the level or walking up a slight hill
3	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
4	Stops for breath after walking ~90 m or after a few minutes on the level
5	Too breathless to leave the house or breathlessness when dressing or undressing
Borg scale	
0	No breathlessness at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight breathlessness
3	Moderate
4	Somewhat severe
5	Severe breathlessness
6	
7	Very severe breathlessness
8	
9	Very, very severe (almost maximum)
10	Maximum

one had ever experienced or could imagine experiencing'. Using the Borg scale, subjects rate the magnitude of their perceived breathing discomfort during exercise. Though somewhat less popular, the visual analogue scale (VAS) is another dyspnoea measuring instrument with proven construct validity during CPET. Both the VAS and Borg scale have been shown to provide similar scores during CPET, and to be reliable and reproducible over time in healthy subjects and in patients with asthma and COPD undergoing CPET.

Physiology

The recent American Thoracic Society and European Respiratory Society statements have emphasised the multidimensional nature of dyspnoea in the sensory–perceptual (intensity and quality), affective distress and impact domains. To gain more insight into our understanding of dyspnoea, a case can be made for answering the following questions.

1) What is the role of mechanical factors and ventilatory constraints in dyspnoea?
2) What are the neurophysiological underpinnings of the most selected cluster descriptors that define the qualitative dimension of dyspnoea in patients?
3) Do obstructive and restrictive lung diseases share some common underlying mechanisms?

Dyspnoea is perceived as a sense of effort

During voluntary increase in ventilation, the motor cortex increases the outgoing motor signal to respiratory muscles and conveys a copy (central corollary discharge) through cortical interneurons to the sensory/association cortex, which is informed of the voluntary effort to increase ventilation (V'_E). It is also likely that the sense of the respiratory effort arises from the simultaneous activation of the sensory cortex and muscle contraction: a variety of muscle receptors provides feedback to the central nervous system about force and tension, and information from these receptors may conceivably underlie the sense of effort. For clinical purposes, the perceived magnitude of respiratory effort is expressed by the ratio of the tidal oesophageal pressure (P_{oes}) to the maximal pressure generation capacity of the respiratory muscles (P_{Imax}). In healthy subjects, volitional respiratory effort is matched by lung/chest wall displacement (*i.e.* change in tidal volume (V_T) as percentage of vital capacity (VC)) *via* concurrent afferent proprioceptive information, transmitted *via* vagal, glossopharyngeal, spinal and phrenic nerves, that monitors displacement, and is processed and integrated in the sensory cortex. The result is a harmonious neuromechanical coupling with avoidance of respiratory discomfort or distress (figure 1 and table 1).

Dyspnoea is perceived as a sense of air hunger

Under some clinical and experimental circumstances, the relationship between dyspnoea and effort is less apparent. If normal subjects suppress their ventilation to a level below that dictated by chemical drive (carbon dioxide), dyspnoea increases without corresponding increases in indices of respiratory effort. Likewise, in experimental and clinical conditions where peripheral stretch receptors are inhibited, the sensory cortex is not informed of the ventilatory response. In these circumstances, dyspnoea is perceived as a sensation of air hunger, the intensity of which depends on a mismatch between the level of chemically stimulated drive and ongoing inhibition from pulmonary mechanosensors signalling the current level of ventilation. In turn, dyspnoea arises and may qualitatively change when peripheral afferent feedback is altered and inspiratory motor output either increases or stabilises.

Pathophysiology

COPD

Two qualitative descriptor clusters of dyspnoea are commonly selected by patients with COPD during physical activity.

The descriptor cluster that alludes to increased respiratory work/effort ('breathing requires more effort or work') is commonly selected by patients with COPD. Increased sense of work/effort is related to the increased motor drive to the respiratory muscles and increased central neural drive (due to chemostimulation) as a consequence of progressive metabolic and ventilation/perfusion disruptions during exercise. Therefore, increased perceived work/effort during physical activity, in part, reflects the greater ventilatory demand for a given task compared with health. In addition, contractile muscle effort is increased for any given ventilation because of:

1) the acutely increased intrinsic mechanical (elastic/threshold) loading; and

2) functional respiratory muscle weakness.

These respiratory mechanical/muscular abnormalities are, in part, related to resting and dynamic hyperinflation during exercise, and may lead to either a decrease in P_{Imax} or a further increase in P_{oes} as a percentage of P_{Imax}. Because of these effects, greater neural drive or electrical activation of the respiratory muscle is required to generate a given force. Furthermore, because of limbic system activation, the corollary discharge may be sensed as abnormal, thus evoking a sensation of distress (figure 1 and table 1).

The other descriptor cluster alludes to unsatisfied inspiration. Structural abnormalities (chronic bronchitis and emphysema), *via* their negative physiological consequences, *i.e.* expiratory flow limitation and dynamic hyperinflation (measured during exercise as a reduction in inspiratory capacity (IC)), result in dyspnoea. A patient's physical activity is characterised by a growing mismatch between increase in central neural output to the respiratory muscles and the blunted respiratory mechanical/muscular response (lung/chest wall displacement). This mismatch, which we call neuroventilatory dissociation (NVD), has been proposed to be, at least in part, the neurophysiological basis of the perceived unsatisfied inspiration. In a clinical setting, the slope that defines NVD (*i.e.* effort *versus* displacement) is steeper and shifted upward compared with healthy subjects. The steeper the slope, the greater the intensity of dyspnoea (figure 2). In particular, patients experience intolerable dyspnoea during exercise because V_{T} expansion is constrained from below (by the effects of dynamic lung hyperinflation or the already critically reduced resting IC), as there is no space to breathe. This so-called dyspnoea threshold seems to be at the level at which the inspiratory reserve volume (IRV) critically approaches 0.5–0.4 L. Once this critical IRV is achieved, further expansion in V_{T} is negated, the effort–volume displacement ratio ($P_{\mathrm{oes}}/P_{\mathrm{Imax}}$ divided by $V_{\mathrm{T}}/\mathrm{VC}$) increases sharply and dyspnoea intensity rises steeply to intolerable levels. The data support the central importance of mechanical restriction in causing dyspnoea in COPD patients.

Neuromuscular disorders

Patients with neuromuscular disorder (NMD) exhibit heightened neuromotor output, which is sensed as increased respiratory muscle effort and, as such, is likely to be the principal mechanism of dyspnoea in NMD. Nonetheless, a significant positive relationship between increased dyspnoea per unit increase in ventilation

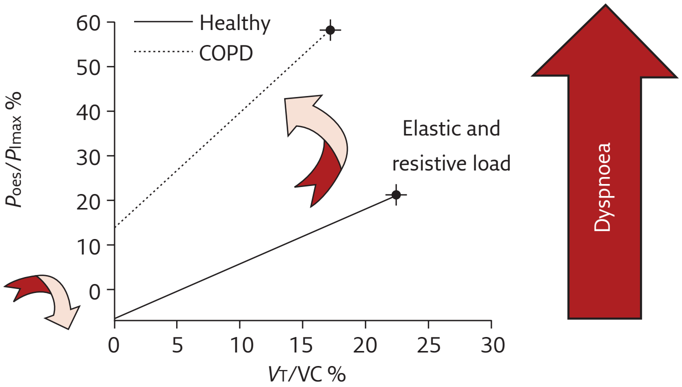


Figure 2. NVD. The slope that defines the mismatch between increase in neural output (inspiratory effort, i.e. P_{oes}/P_{Imax}*) and lung/chest wall displacement (*V_T/VC*) is steeper and shifted upwards in patients with COPD compared with healthy subjects.*

and dynamic elastance affects the coupling between respiratory effort and displacement (figure 3).

Interstitial lung disease

As in COPD, restrictive dynamic respiratory mechanics limits the ability of patients with interstitial lung disease (ILD) to increase ventilation in response to the increased metabolic demands of physical tasks. One of the characteristic features of ILD is a reduction in lung compliance and lung volumes. This has two major consequences:

1) greater pressure generation is required by the inspiratory muscles for a given V_T;

2) the resting TLC and IRV are often diminished compared with health.

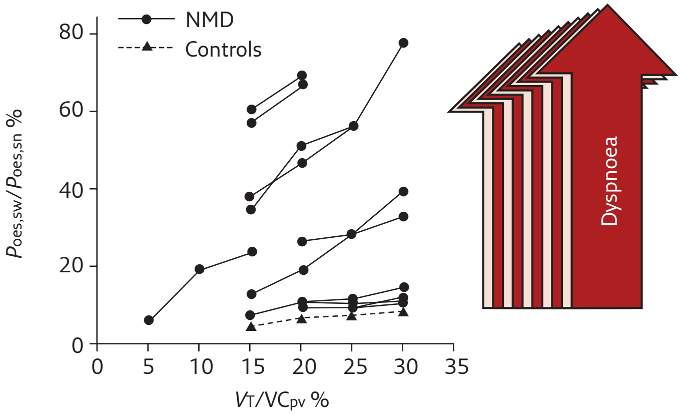


Figure 3. A mismatch between inspiratory effort (swing in oesophageal pressure ($P_{oes,sw}$*) as a percentage of oesophageal pressure during a sniff manoeuvre (*$P_{oes,sn}$*)) and lung/chest wall displacement (*V_T *as a percentage of the predicted value of the vital capacity (*VC_{pv}*)) in patients with NMD compared with average data from controls. The steeper the slope, the greater the perception of dyspnoea.*

Therefore, V_T expansion is constrained from above early in exercise (reflecting the reduced TLC and IRV), which results in greater reliance on increasing breathing frequency to increase ventilation. Differences in dynamic ventilatory mechanics, including possible expiratory flow limitation in some patients, account for distinct qualitative perception in ILD patients, namely inspiratory difficulty/unsatisfied inspiration and rapid shallow breathing. Because of increases in both dynamic elastance and efferent respiratory drive, inspiratory difficulty/unsatisfied inspiration may have its neurophysiological basis in the conscious awareness of a dissociation between the increased drive to breathe (and concurrent increased respiratory effort, *i.e.* P_{oes}/P_{Imax}) and the restricted mechanical response of the respiratory system (*i.e.* V_T/VC), *i.e.* the inability to expand V_T appropriately in the face of an increased drive to breathe. In turn, the possibility has also been put forward that intensity of exertional dyspnoea in ILD is more closely linked to mechanical constraints on volume expansion than to indexes of inspiratory effort *per se*.

Chronic heart failure

The key message that has emerged from therapeutic intervention studies in patients with chronic heart failure (CHF) is that exertional dyspnoea alleviation is consistently associated with reduced excessive ventilatory demand (secondary to reduced central neural drive), improved respiratory mechanics and muscle function and, consequently, enhanced neuromechanical coupling of the respiratory system during exercise. Pressure support is reported to reduce the tidal inspiratory pleural pressure–time slope without affecting submaximal dyspnoea ratings, but allows patients to exercise for additional time without experiencing any significant rise in dyspnoea. The available data suggest that increased ventilatory demand, abnormal dynamic ventilatory mechanics and respiratory muscle dysfunction are instrumental in causing exertional dyspnoea in patients with severe cardiac impairment.

Obesity

An increase in respiratory neural drive is deemed to be the reason for the similar increase in dyspnoea in obese and lean subjects. However, different underlying mechanisms may affect dyspnoea in obese subjects. Exercise performance is impaired compared with healthy, normal-weight subjects when corrected for the increased lean body mass, but normal when expressed as a percentage of predicted for ideal body weight in subjects who hyperinflate their lungs to the same extent as those obese subjects who deflate their lungs, with both volume subgroups reaching similar dyspnoea scores. In ‘hyperinflators’, dynamic hyperinflation, along with a decrease in IRV, increases respiratory muscle loading, respiratory drive and perception of respiratory discomfort. In contrast, ‘deflators’ exhibit a negative relationship between resting end-expiratory lung volume (EELV) and perceptual respiratory response during exercise: the lower the EELV, the greater the Borg score. A low EELV has three important consequences that link together during exercise:

1) decrease in expiratory reserve volume;

2) dynamic airway compression; and

3) changes in transmural airway pressure resulting in airway dynamic compression.

Thus, an alteration in the central drive to the respiratory muscles in response to afferent activity from upper airway mechanoreceptors may also contribute to the unpleasant respiratory sensation in obese subjects.

Asthma

Three dominant qualitative descriptors of exertional dyspnoea emerge in patients with asthma: 1) chest tightness; 2) increased work/effort ('breathing requires more work or effort'); and 3) unsatisfied/unrewarded inspiration ('can't get enough air in'). It has been pointed out that regardless of the global score of intensity of dyspnoea, different descriptors may be selected by asthmatic patients during short cycle exercise sessions and methacholine challenge test. Airway obstruction and dynamic lung hyperinflation, as measured by the decrease in IC, correlates best with dyspnoea during methacholine challenge test. Chest tightness is the highest reported descriptor (68%) during methacholine inhalation. During short cycle exercise V'_E is the best predictor of dyspnoea, and work/effort is the highest reported descriptor (72%). IC may decrease in a subgroup of asthmatic patients during exercise. Of interest, this subgroup of patients shows a similar degree of hyperinflation during methacholine challenge test, but their description of dyspnoea is different between the two tests: during methacholine challenge test, 60% of the responses are chest tightness, 10% inspiratory effort and 30% are expiratory effort; during exercise, 90% are inspiratory effort and 10% chest tightness. More recently, it has been argued that the presence of expiratory flow limitation at rest and during exercise may be explained by the significant decrease in IC (*i.e.* dynamic lung hyperinflation) observed in a subgroup of patients with stable mild asthma undergoing high-intensity constant work-rate cycle exercise. A strong correlation is found between the extent of expiratory flow limitation and the reduction in IC (expressed as % of predicted TLC) during exercise ($r=-0.82$, $p=0.04$). The quantitative and qualitative aspects of dyspnoea in patients with asthma may also be evaluated. In this regard, it has been showed that even mild stable asthmatics are able to perceive critical mechanical constraints on V_T expansion during exercise. It has been demonstrated that V_T expansion becomes constrained due to dynamic lung hyperinflation at a critically reduced IRV only in 37.5% of subjects and it marks the point where dyspnoea intensity rises abruptly and there is a transition in the dominant qualitative descriptor choice from work/effort to difficult/unsatisfied inspiration. By contrast, V_T expansion flattens at a preserved IRV in 62.5% of subjects and it does not mark a mechanical event with important sensory consequences. The corollary of this is that therapeutic interventions that effectively delay the appearance of the V_T constraints at a critically reduced IRV should theoretically reduce the attendant dyspnoea during physical activity even in patients with mild stable asthma. The clinical relevance of these findings is that, pending confirmation in larger samples, by asking about the quality of dyspnoea at the end of an exercise bout one can ascertain whether a critical IRV has been reached (difficult/unsatisfied inspiration) or not (work/effort), *i.e.* the likelihood of developing exercise-related critical volume constraints in asthmatic patients.

Pulmonary arterial hypertension

Exertional dyspnoea is by far the dominant symptom in patients with pulmonary arterial hypertension (PAH). Recent advances in PAH have clearly demonstrated that some PAH patients (up to 60%) may exhibit reduced expiratory flows in tidal operating range, which could promote exercise-induced dynamic lung hyperinflation. Few studies have examined the impact of potential dynamic lung hyperinflation-induced critical mechanical constraints on the intensity of dyspnoea in young nonsmoking patients with idiopathic and heritable PAH undergoing symptom-limited incremental CPET. Using spirometry, these studies showed that reduced expiratory flows at low lung volumes exist in a large proportion of idiopathic and heritable PAH patients (60%) despite a preserved FEV_1/VC ratio. When increased ventilation/perfusion mismatching is superimposed on pre-existing abnormal airway function, greater troublesome exertional symptoms ensue. Although dyspnoea in these patients is probably multifactorial, these results clearly indicate that increased ventilatory demand and abnormal dynamic ventilatory mechanics should be considered in PAH patients, in the absence of respiratory muscle dysfunction or TLC changes.

Asymptomatic subjects with airway obstruction

In at-risk subjects who complain of symptoms, early detection of COPD has been proven to be effective and is now recommended. Nevertheless, this strategy is unable to detect COPD in subjects who do not report any symptoms. COPD screening programmes in asymptomatic at-risk individuals have, therefore, been evaluated. Identifying airway obstruction, as defined by an FEV_1/FVC ratio below the fixed cut-off of 0.70 in asymptomatic subjects, does not appear to be beneficial because they do not have an accelerated decline in FEV_1 and are not at higher risk of premature death. In contrast, even in the absence of COPD-related symptoms, subjects with persistent airway obstruction defined by a post-bronchodilator FEV_1/FVC ratio below the statistically based, age-specific lower limit of normal (LLN) are at risk of premature death and/or of development of respiratory symptoms, suggesting that their identification is pertinent. It has recently been demonstrated that subjects with mild airway obstruction, defined as post-bronchodilator FEV_1/FVC <LLN together with normal FEV_1, who do not complain of any COPD symptom had, however, greater dyspnoea intensity during incremental exercise and poorer peak exercise capacity than matched healthy subjects with normal spirometry; these asymptomatic subjects with airway obstruction had a greater reduction in IC than healthy controls during exercise, and half of them had significant dynamic lung hyperinflation on exertion.

Mild COPD

Symptomatic smokers with only modest physiological abnormalities at rest might present with activity-related dyspnoea leading to chronic inactivity restriction, reduced health-related quality of life and poorer prognosis. A number of physiological anomalies at rest have the potential to impact on exercise responses in patients with mild COPD: increased peripheral airways resistance; heterogeneous distribution of alveolar ventilation; expiratory flow-limitation (EFL), pulmonary gas trapping and reduced IC; increased alveolar–arterial oxygen tension difference; and low T_{LCO} and transfer coefficient. During exercise, a decreased ventilatory efficiency (increased V'_{E}/carbon dioxide output (V'_{CO_2}) nadir and a steeper $V'_{\text{E}}/V'_{\text{CO}_2}$ slope) compared with healthy controls, reflecting heightened chemostimulation due to high physiological dead space, and dynamic lung hyperinflation secondary to EFL and high ventilatory demand can be found. The combination of reduced IC and high inspiratory neural drive may result in early attainment of critical mechanical constraints and higher exertional dyspnoea ratings compared with age-matched healthy controls.

Effects of interventions on dyspnoea

Effective improvement in exertional dyspnoea represents one of the most challenging targets of management in patients with cardiopulmonary disease. Traditionally, the approach to improving exertional dyspnoea in all of the major cardiopulmonary diseases involves interventions that:

1) reduce ventilatory demand (by reducing the drive to breathe);
2) improve ventilatory capacity;
3) improve respiratory mechanics (by reducing the mechanical load);
4) increase the functional strength of weakened ventilatory muscles;
5) address the affective dimension of dyspnoea; and
6) any combination of the above.

It is noteworthy that interventions should be selected based on the underlying pathophysiological background of the specific disease under examination and may differ from one disease to another. However, multiple interventions are generally required and appear to have additive or synergistic effects.

Some of these interventions include the following:

- Bronchodilators
- Oxygen
- Heliox
- Exercise training
- Biventricular pacing (specifically for CHF patients)
- Biofeedback techniques
- NIV
- Lung volume reduction surgery and related endoscopic techniques
- Various combinations of these interventions

All of the above strategies have been proven to provide beneficial sensory consequences in a variety of patients with cardiopulmonary diseases.

In selected patients, interventions such as opiates (oral and inhaled) reduce respiratory drive and alter affective components of dyspnoea. Recently, it has been shown that inhaled furosemide may modulate respiratory sensation by altering afferent inputs from vagal receptors within the lungs. Psychological counselling, cognitive/behavioural modification and anxiolytics can have favourable influences on the affective dimension of chronic dyspnoea.

Conclusion

We are still a long way from understanding the symptom of dyspnoea. Although mechanical factors are important contributors to dyspnoea, the precise mechanisms of dyspnoea remain obscure. One approach to the study of this symptom is to identify the major qualitative dimensions of the symptom in an attempt to uncover different underlying neurophysiological mechanisms. The remarkable similarity in choices of qualitative descriptors (work/effort, inspiratory difficulty/unsatisfied inspiration, air hunger and rapid breathing) for exertional dyspnoea in patients with restrictive and obstructive syndromes raises the intriguing possibility that they share some common underlying mechanisms.

Further reading

- Guenette JA, *et al.* (2012). Does dynamic hyperinflation contribute to dyspnoea during exercise in patients with COPD? *Eur Respir J*; 40: 322–329.
- Killian KJ, *et al.* (1995). Dyspnoea. *In*: Roussos C, ed. The Thorax, part B. New York, Dekker; pp. 1709–1747.
- Lanini B, *et al.* (2001). Perception of dyspnea in patients with neuromuscular disease. *Chest*; 120: 402–408.
- Laveneziana P, *et al.* (2006). Mechanisms of dyspnoea and its language in patients with asthma. *Eur Respir J*; 27: 742–747.
- Laveneziana P, *et al.* (2009). Effect of biventricular pacing on ventilatory and perceptual responses to exercise in patients with stable chronic heart failure. *J Appl Physiol*; 106: 1574–1583.
- Laveneziana P, *et al.* (2011). Evolution of dyspnea during exercise in chronic obstructive pulmonary disease: impact of critical volume constraints. *Am J Respir Crit Care Med*; 184: 1367–1373.
- Laveneziana P, *et al.* (2013). Dynamic respiratory mechanics and exertional dyspnoea in pulmonary arterial hypertension. *Eur Respir J*; 41: 578–587.
- Laveneziana P, *et al.* (2013). Tidal volume inflection and its sensory consequences during exercise in patients with stable asthma. *Respir Physiol Neurobiol*; 185: 374–379.
- Laveneziana P, *et al.* (2015). Inspiratory muscle function, dynamic hyperinflation and exertional dyspnoea in pulmonary arterial hypertension. *Eur Respir J*; 45: 1495–1498.
- Laviolette L, *et al.* (2014). Dyspnoea: a muldimensional and multidisciplinary approach. *Eur Respir J*; 43: 1750–1762.
- O'Donnell DE, *et al.* (1997). Qualitative aspects of exertional breathlessness in chronic airflow limitation: pathophysiologic mechanisms. *Am J Respir Crit Care Med*; 155: 109–115.
- O'Donnell DE, *et al.* (1998). Qualitative aspects of exertional dyspnoea in patients with interstitial lung disease. *J Appl Physiol*; 84: 2000–2009.
- O'Donnell DE, *et al.* (2006). Sensory-mechanical relationships during high intensity, constant-work-rate exercise in COPD. *J Appl Physiol*; 101: 1025–1035.
- Ofir D, *et al.* (2007). Ventilatory and perceptual responses to cycle exercise in obese females. *J Appl Physiol*; 102: 2217–2226.
- Ofir D, *et al.* (2008). Mechanisms of dyspnea during cycle exercise in symptomatic patients with GOLD stage I chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 177: 622–629.
- Parshall MB, *et al.* (2012). An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med*; 185: 435–452.
- Romagnoli I, *et al.* (2008). Role of hyperinflation *vs* deflation on dyspnea in severely to extremely obese subjects. *Acta Physiol*; 193: 393–402.
- Soumagne T, *et al.* (2016). Asymptomatic subjects with airway obstruction have significant impairment at exercise. *Thorax*; 71: 801–811.

Chest pain

Matthew Hind

Chest pain is a frequent symptom of illness and a common reason for seeking medical attention. Rapid assessment is crucial so that life-threatening diseases, such as cardiac chest pain, aortic dissection and oesophageal rupture, can be identified and managed appropriately. A basic history often points to the cause and is used in triage of patients attending emergency rooms. Questions are typically asked about the character, location, radiation, severity, exacerbating and relieving factors, and relationship to movement such as breathing or coughing. Objective assessment using a questionnaire, such as the McGill Pain score (Melzack, 1975), can be helpful. Occasionally, it is difficult to tease out differences between cardiac, gastrointestinal and respiratory causes of pain. The use of screening tools, questionnaires, electrocardiograms and serial troponin measurements can accurately stratify patients to assist clinical decision making.

The pathophysiology of chest pain is complex and not completely understood, but involves peripheral nociceptors, either small Aδ myelinated or unmyelinated C afferent fibres that project *via* sympathetic and parasympathetic nerves into the dorsal horn of the spinal cord. These neurons synapse with spinothalamic fibres which ascend, cross the spinal cord and terminate in the contralateral ventral posterior thalamic nucleus. Thalamocortical neurons project *via* the posterior limb of the internal capsule to the somatosensory cortex. The diaphragm has dual nociceptive sensory innervation from both the phrenic nerve and the lower six intercostal nerves; therefore, diaphragmatic irritation can present with pain referred to either the shoulder or upper abdomen. The trachea and large airways have afferent fibres that project along the vagus nerve. Respiratory chest pain can therefore originate from the chest wall, pleura, large airways and mediastinum but visceral 'lung' pain is unusual.

Pleural pain is often described as sharp, stabbing and made worse with movement such deep respiration. The pain is often unilateral, reflecting the site of disease. A pleural rub may be heard. Pleuritic pain with sudden onset suggests a diagnosis of pulmonary emboli, pulmonary infarction or pneumothorax, whereas pleuritic pain building over a few hours may suggest infection, such as pneumonia or pleurisy. Onset over several days suggests empyema, malignancy or TB.

Key points

- Chest pain can be a feature of a wide range of pathologies.
- An accurate history is essential to direct appropriate investigation of patients presenting with chest pain.

Tracheobronchitis can present with a midline burning pain made worse with respiration. Massive mediastinal lymphadenopathy can cause an indistinct, heavy central chest pain. Similarly, chest pain associated with pulmonary hypertension can be difficult to distinguish from cardiac chest pain. Nondescript, heavy chest pain is quite common in exacerbations of bronchiectasis.

Chest wall pain is usually well localised, reproduced with movement and associated with tenderness. Costocondritis and Tietze's syndrome are inflammatory disorders of the thoracic joints that present with chest wall pain and tenderness. Bornholm disease (epidemic pleurodynia or devil's grip), often associated with Coxsackie B virus, can present with epidemics of chest wall pain of sudden onset.

Neuralgic pain can be sharp and knife-like or dull and heavy, and there may be associated sensory symptoms. Pain in a dermatomal distribution requires examination of overlying skin for the characteristic vesicular rash of herpes zoster.

ECG is essential for immediate assessment of cardiac chest pain. Further investigation may include exercise ECG, stress echocardiography or myocardial perfusion imaging. Angiography offers the opportunity for intervention with angioplasty and stent insertion.

Chest radiographs are useful to identify consolidation, pneumothorax, pleural effusion and bony abnormalities such as vertebral fractures. Contrast CT scanning has made identification of pulmonary emboli, aortic dissection and oesophageal rupture straightforward, and can identify abnormalities often missed on plain radiographs. Nuclear medicine scans have a role in both diagnosis and management of pulmonary emboli. Bone scintigraphy is useful in evaluation of 'bony' pain. MRI examination is of particular use in visualising nerve roots, the heart and soft tissues of the mediastinum. Direct endoscopic visualisation of either the upper gastrointestinal tract (oesophagogastroduodenoscopy) or major airways (bronchoscopy) allows epithelial inspection and offers the opportunity for direct microbiological, cytological and histological sampling.

Further reading

- Mark DG, *et al.* (2018). Performance of coronary risk scores among patients with chest pain in the emergency department. *J Am Coll Cardiol*; 71: 606–616.
- Melzack R. (1975). The McGill Pain Questionnaire: major properties and scoring methods. *Pain*; 1: 277–299.

Cough and sputum

Alyn H. Morice

Cough is a vital protective mechanism defending the airways from inhalation and aspiration. Patients with a defective cough reflex, such as those with stroke or Parkinson's disease, have an increase in mortality and morbidity caused by the increased propensity for aspiration. However, in lung disease cough is often not helpful, and is the result of hypersensitivity of the vagal afferent nerves. Thus, in the commonest form of cough, that due to upper respiratory tract infection, coughing serves no useful purpose from the sufferer's point of view, but aids viral transmission. In chronic cough, the frequency and severity of coughing bouts may cause serious disruption to the patient's life. Quality-of-life instruments have indicated that patients with chronic cough have a similar decrement to that seen with conditions such as cancer and severe COPD. Cough also causes significant comorbidity. Chronic cough is commonest in middle aged women and 50% attending cough clinics are incontinent. Cough syncope is responsible for a number of driving fatalities.

Acute cough

Acute cough due to one of the myriad of upper respiratory tract viruses places an enormous demand on the healthcare community. It is the commonest new presentation to primary care, accounting for 50% of consultations. In temperate regions there is a marked seasonal variation with autumn and winter epidemics. Viral transmission requires person-to-person contact, either through airborne droplet infection or the manual passage of secretions. Superimposed on this seasonal pattern are peaks caused by socialisation, *e.g.* return to school for the autumn term and Christmas family gatherings. Apart from general health measures, such as hand washing and avoidance of contact, there is no specific treatment for upper respiratory tract infection-induced cough. The efficacy of the many cough remedies is likely to be due to a physicochemical (demulcent) effect although recent randomised controlled trials have shown some small additional benefit.

Key points

- Cough is characterised by hypersensitivity of the vagal sensory nerves.
- Nonacid reflux into the airways frequently precipitates cough.
- Clinical history followed by therapeutic trials is the management strategy of choice.

Chronic cough

Chronic cough is one of the commonest presentations to the respiratory physician. A meta-analysis of 90 papers reporting the worldwide prevalence of chronic cough suggests that 9.6% of the population complain of cough >8 weeks in duration. A survey of 10 032 patients attending specialist cough clinics found that the typical patient is middle-aged and two-thirds are female. Women have a heightened sensitivity to cough challenge and a larger functional MRI response in the somatosensory cortex to that challenge.

In a patient with normal spirometry and a normal chest radiograph the cough often appears to have no pattern to it but a careful history will often reveal many characteristic features of the presenting complaint. It has been traditional to divide these patients into a triad of diagnoses, namely asthmatic cough, post-nasal drip syndrome (rhino-sinusitis *etc.*) and reflux cough. These subdivisions are now considered redundant. Thus, asthmatic cough is unlike classic atopic asthma in that it is usually of late onset without obvious precipitants and often without evidence of bronchoconstriction. In the form known as eosinophilic bronchitis there is even an absence of bronchial hyperreactivity. Similar caveats apply to post-nasal drip syndrome and reflux cough, the latter frequently not meeting the pH criteria for peptic gastro-oesophageal reflux disease. Because of the commonality of the clinical history in chronic cough, it has been suggested that there is a single unifying diagnosis of cough hypersensitivity syndrome, with the other diagnoses representing different phenotypes of this condition. Thus, each individual presents with a different constellation of symptoms and a unique inflammatory profile. The risk factors for chronic cough suggest that nonacid reflux and oesophageal dysmotility may be an important precipitant (table 1). A validated questionnaire, the Hull Airways Reflux Questionnaire, provides a simple diagnostic tool for airway reflux (table 2).

Virtually all patients presenting with a chronic cough complain of increased sensitivity to a wide range of environmental stimuli. This hypersensitivity can be objectively demonstrated in the laboratory using cough challenge. There is a wide variation in cough reflex sensitivity in normal subjects; with women being more sensitive than men, this heightened sensitivity appears after puberty. Sensitivity is also accentuated in cough patients. A family of nociceptors of the transient receptor potential (TRP) group exemplified by the archetypal capsaicin-sensitive ‘hot’ receptor (TRPV1) are responsible for the perception of the irritant stimuli (figure 1). This knowledge is of great help clinically since the patient can be told they are exhibiting hypersensitivity of airway sensory nerves rather than ‘it’s a mystery’. Another TRP receptor, TRPA1, is highly reactive to a wide range of environmental irritants and is likely to be the major sensor causing the exquisite hypersensitivity complained of by patients to agonists such as acrolein (smoke), eugenol (perfume) and bleach. Rather than directly causing cough, angiotensin-converting enzyme inhibitors increase cough sensitivity thus explaining the continued irritation many months after drug withdrawal as the ‘nocicostat’ resets.

Management of chronic cough

The clinical history (supported by the Hull Airway Reflux Questionnaire) is the key to the diagnosis. All patients presenting with chronic cough undergo spirometry and a chest radiograph. Elevated blood eosinophil count and exhaled nitric oxide fraction may be useful screening tools for the asthmatic/eosinophilic bronchitis phenotype. The European Respiratory Society guidelines recommend therapeutic trials based on clinical judgement.

Table 1. Risk factors for chronic cough

Variable	With cough n/N (%)	Unadjusted OR (95% CI)	p-value
Sex			
Male	78/1704 (4.6)	1.0	
Female	135/2179 (6.2)	1.38 (1.03–1.86)	0.028
Heartburn			
No	148/2990 (4.9)	1.0	
Yes	65/889 (7.3)	1.51 (1.10–2.06)	0.009
Regurgitation			
No	158/3314 (4.8)	1.0	
Yes	54/568 (9.5)	2.10 (1.49–2.92)	<0.0001
Irritable bowel syndrome			
No	111/2914 (3.8)	1.0	<0.0001
Yes	98/909 (10.8)	3.05 (2.27–4.09)	
BMI category			
Normal	74/1547 (4.8)	1.0	
Overweight	72/1448 (5.0)	1.04 (0.74–1.47)	0.86
Obese	60/776 (7.7)	1.67 (1.15–2.41)	0.006

Nonacid reflux symptoms in the form of regurgitation are more closely associated with cough than acid reflux.

Thus, in patients with evidence of eosinophilic inflammation, a trial of asthmatic medication may be beneficial (figure 2). However, as bronchoconstriction is rarely a major component of this phenotype of cough hypersensitivity, long-acting β-agonists may be less effective than leukotriene antagonists. Indeed, inhaled corticosteroids seem less effective than in classic asthma and a trial of oral prednisolone may be required to establish the diagnosis. Biological therapy shows promise.

Reflux disease may be very problematic, as much airway reflux is nonacidic and, therefore, not amenable to blockade by proton-pump inhibitors. Indeed, proton-pump inhibitors may increase the tendency for aspiration. Since oesophageal dysmotility is common, pro-motility agents such as metoclopramide and domperidone may be used. Other motility agents, such as erythromycin and azithromycin, have also been advocated. Operative treatment *via* nissen fundoplication can be effective in intractable coughing, but should only be used in patients without significant dysmotility. An alternative strategy is to treat the hypersensitivity component with agents such as gabapentin, however, clinical experience has been disappointing. Alternatively, the use of central cough suppression in the form of antitussive agents, such as low-dose morphine, has proven highly successful but is only effective in one-third of patients. There is good evidence that speech physiotherapy, when correctly undertaken, can reduce cough and improve quality of life.

The dramatic effect of the P2X3 receptor antagonist gefapixant (AF 219/MK 7264) in clinical trials has proven a great stimulus to cough therapeutics. There are now at least seven different drugs in late stage development. P2X3 is an ATP receptor located on afferent nerves and its blockade causes a reduction in cough counts and an improvement in quality of life in approximately 75% of patients with otherwise

Table 2. Hull airway reflux questionnaire

HULL AIRWAY REFLUX QUESTIONNAIRE

Name: ______________________________

D.O.B: ____________________ UN: ____________________

DATE OF TEST: ______________________________

Please circle the most appropriate response for each question

Within the last MONTH, how did the following problems affect you?

0=no problem and 5=severe/frequent problem

Hoarseness or a problem with your voice	0	1	2	3	4	5
Clearing your throat	0	1	2	3	4	5
The feeling of something dripping down the back of your nose or throat	0	1	2	3	4	5
Retching or vomiting when you cough	0	1	2	3	4	5
Cough on first lying down or bending over	0	1	2	3	4	5
Chest tightness or wheeze when coughing	0	1	2	3	4	5
Heartburn, indigestion, stomach acid coming up (or do you take medications for this, if yes score 5)	0	1	2	3	4	5
A tickle in your throat, or a lump in your throat	0	1	2	3	4	5
Cough with eating (during or soon after meals)	0	1	2	3	4	5
Cough with certain foods	0	1	2	3	4	5
Cough when you get out of bed in the morning	0	1	2	3	4	5
Cough brought on by singing or speaking (for example, on the telephone)	0	1	2	3	4	5
Coughing more when awake rather than asleep	0	1	2	3	4	5
A strange taste in your mouth	0	1	2	3	4	5

TOTAL SCORE /70

Hull Airway Reflux Questionnaire: a diagnostic questionnaire for nonacid reflux. Upper limit of normal <14. © A. Morice.

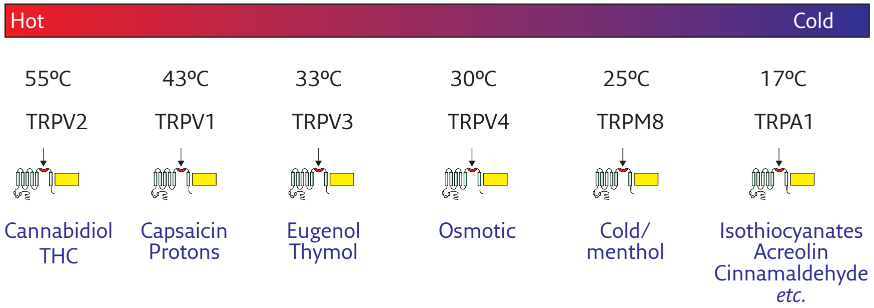

Hot
Cold
55ºC
43ºC
33ºC
30ºC
25ºC
17ºC
TRPV2
TRPV1
TRPV3
TRPV4
TRPM8
TRPA1
Cannabidiol
THC
Capsaicin
Protons
Eugenol
Thymol
Osmotic
Cold/
menthol
Isothiocyanates
Acreolin
Cinnamaldehyde
etc.

Figure 1. The thermosensitive TRP channels that are important in cough reflex sensitivity. Typical 'natural' agonists are listed below each channel. THC: tetrahydrocannabinol.

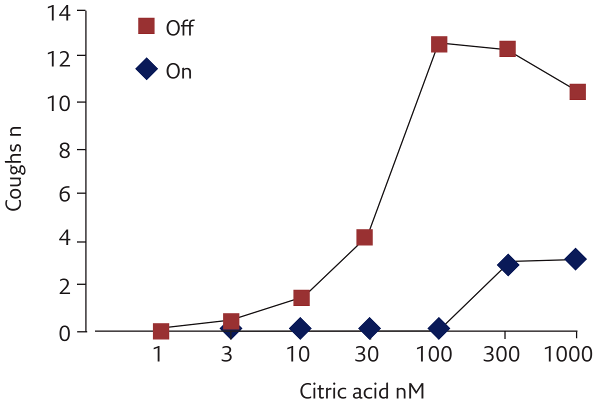


Figure 2. Cough challenge with citric acid in eosinophilic bronchitis and the response to inhaled steroids. Number of coughs off and on budesonide is shown.

intractable cough. Release of ATP by damaged airways is now thought to be a major mechanism underlying cough hypersensitivity.

Sputum

In subjects with chronic cough, production of moderate amounts of sputum does not alter the diagnostic profile. The separation from individuals with excessive sputum production is arbitrary, but is generally regarded as a cup of sputum per day. Above this limit, a diagnosis of bronchiectasis becomes increasingly likely. The presence of sputum purulence indicates a greater likelihood but does not seem to predict the degree of anatomical damage to the airway. Indeed, the diagnosis of bronchiectasis, relying as it does on the dilation and destruction of the airways, will not include many patients with functional abnormalities of the bronchi.

In conditions characterised by sputum hypersecretion, there is usually a change in the composition of the mucus. Several mechanisms are responsible for this change. Thus, in CF, the increase in sodium reabsorption leads to a reduction in the sol phase of the airway surface liquid. Airway inflammation, particularly that caused by release of enzymes such as myeloperoxidase (which produces the characteristic green colour) and neutral endopeptidase, and by polymorphs, causes alteration of the mucin (*MUC*) gene expression through proteinase-activated receptors. The death of inflammatory cells, releasing DNA to form neutrophil extracellular traps, leads to a soup of DNA that cross-links with filamentous actin, producing gelatinous plugs that increase ventilation/perfusion ratio mismatch with resulting systemic hypoxia.

The treatment of mucus hypersecretion may be challenging. In the presence of purulent sputum, every effort should be made to identify the causative organism. Persistent bacterial bronchitis is a recently recognised condition, particularly prevalent in children. Eradication with appropriate high-dose antibiotic therapy may lead to sustained remission. More frequently, there is rapid relapse, indicating the need for maintenance antibiotics either orally or *via* the nebulised route. The advantage of this latter strategy is that side-effects may be minimised by using agents with high local potency but poor oral bioavailability, such as colomycin or tobramycin. Antioxidant mucolytics are widely prescribed but evidence of efficacy is limited. The largest study of *N*-acetylcysteine over 3 years showed no effect on decline in lung function or exacerbation rate. In COPD,

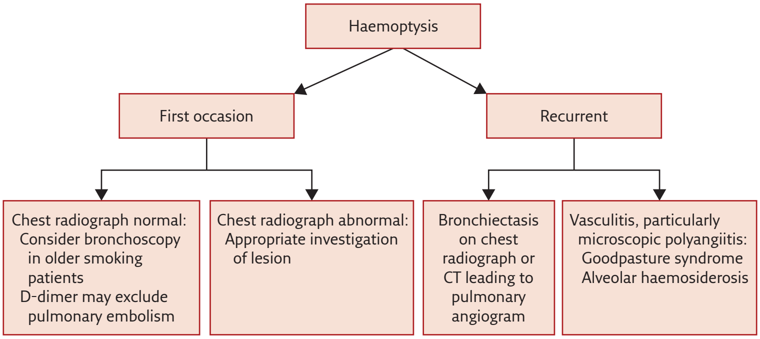

Haemoptysis
First occasion
Recurrent
Chest radiograph normal: Consider bronchoscopy in older smoking patients
D-dimer may exclude pulmonary embolism
Chest radiograph abnormal: Appropriate investigation of lesion
Bronchiectasis on chest radiograph or CT leading to pulmonary angiogram
Vasculitis, particularly microscopic polyangiitis: Goodpasture syndrome
Alveolar haemosiderosis

Figure 3. A flow diagram of the management strategy for haemoptysis. NB: check for coagulopathy.

two agents, azithromycin and roflumilast, have been shown to be efficacious in those with exacerbations of chronic bronchitis. Azithromycin has also been shown to reduce exacerbation rates in bronchiectasis and CF.

Perhaps because of the paucity of specific agents for mucus hypersecretion, nonpharmacological therapy in the form of airway clearance techniques is frequently advocated. However, a recent Cochrane review found the quality of randomised studies to be poor and concluded that any benefits achieved may be small. A much better evidence base exists for the use of nebulised hypertonic saline.

Haemoptysis

Haemoptysis presents in two clinical scenarios (figure 3). First, the patient may present with *de novo* haemoptysis without pre-existing lung disease. Any mucosal lesion may cause haemoptysis of small amounts of blood mixed with sputum. Since this is a common presentation of lung cancer, chest radiography is obligatory in patients presenting with haemoptysis and, in heavy smokers, CT or bronchoscopy is also required. Aspergilloma and TB may similarly cause blood-stained bronchitis. More peripheral lung pathology, such as lobar pneumonia, gives rise to sputum that is frequently described as ‘rusty’. Haemoptysis of frank blood is a common sign of pulmonary embolism or infarction.

Obviously, recurrent haemoptysis initially presents with acute haemoptysis. Typically, bronchiectasis leads to recurrent, sometimes massive and occasionally fatal haemoptysis. The bronchial blood supply arises from the aorta and, in contrast to the pulmonary circulation, is at systemic pressure. In bronchiectasis, there is hypertrophy of the bronchial arteries as a consequence of recurrent infection. When the patient presents with life-threatening haemoptysis, radiographic percutaneous bronchial artery embolisation is the treatment of choice. Vasculitis is a common and frequently missed cause of recurrent haemoptysis and diffuse alveolar haemorrhage. While the systemic connective tissue diseases, such as systemic lupus erythematosus, may produce small-vessel haemoptysis, the commonest cause is microscopic polyangiitis. The perinuclear anti-neutrophil cytoplasmic antibody is positive in ~70% of cases. Finally, haemoptysis may be the result of alveolar haemorrhage. Disease of the vascular or alveolar wall, such as Goodpasture’s syndrome or alveolar haemosiderosis, may present with recurrent haemoptysis. Clearly, disorders of coagulation, both congenital and acquired, and including warfarin or direct-acting oral anticoagulant therapy, thrombocytopenia and coagulopathies will predispose to haemoptysis.

Further reading

- Abdulqawi R, *et al.* (2015). P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet*; 385: 1198–1205.
- Albert RK, *et al.* (2011). Azithromycin for prevention of exacerbations of COPD. *N Engl J Med*; 365: 689–698.
- Birrell MA, *et al.* (2009). TRPA1 agonists evoke coughing in guinea-pig and human volunteers. *Am J Respir Crit Care Med*; 180: 1042–1047.
- Chamberlain SA, *et al.* (2015). The impact of chronic cough: a cross-sectional European survey. *Lung*; 193: 401–408.
- Decramer M, *et al.* (2005). Effects of *N*-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet*; 365: 1552–1560.
- Ford AC, *et al.* (2006). Cough in the community: a cross sectional survey and the relationship to gastrointestinal symptoms. *Thorax*; 61: 975–979.
- Kahrilas PJ, *et al.* (2016). Chronic cough due to gastroesophageal reflux in adults: CHEST guideline and expert panel report. *Chest*; 150:1341–1360.
- Morice AH, *et al.* (2004). The diagnosis and management of chronic cough. *Eur Respir J*; 24: 481–492.
- Morice AH, *et al.* (2007). Opiate therapy in chronic cough. *Am J Respir Crit Care Med*; 175: 312–315.
- Morice AH, *et al.* (2010). The cough hypersensitivity syndrome: a novel paradigm for understanding cough. *Lung*; 188: 87–90.
- Morice AH, *et al.* (2011). Cough hypersensitivity syndrome: a distinct clinical entity. *Lung*; 189: 73–79.
- Morice AH, *et al.* (2014). A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. *Eur Respir J*; 44: 1149–1155.
- Morice AH, *et al.* (2014). Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. *Eur Respir J*; 44: 1132–1148.
- Osadnik CR, *et al.* (2012). Airway clearance techniques for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*; 3: CD008328.
- Rogers DF (2007). Physiology of airway mucus secretion and pathophysiology of hypersecretion. *Respir Care*; 52: 1134–1146.
- Sadeghi MH, *et al.* (2018). Does *F*eNO predict clinical characteristics in chronic cough? *Lung*; 196: 59–64.
- Song WJ, *et al.* (2015). The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. *Eur Respir J*; 45: 1479–1481.
- Vertigan AE, *et al.* (2006). Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. *Thorax*; 61: 1065–1069.

Physical examination

Martyn R. Partridge

Physical findings in the context of the history

The purpose of clinical assessment is to make an accurate diagnosis. Making an accurate diagnosis in cases of respiratory disease can be challenging, not only because of the diversity of respiratory ill health but also because the symptoms of respiratory disease are shared with disorders of other body systems.

Breathlessness (a sensation of difficult, laboured or uncomfortable breathing) may have a physiological, pathological or psychological explanation, but it is extremely important that every time we are faced with a patient complaining of shortness of breath we consider the following.

Is this patient breathless because of:

- heart disease,
- lung disease,
- pulmonary vascular disease,
- a systemic disorder (anaemia, obesity or hyperthyroidism), or
- respiratory muscle weakness?

It is vital that we go through this checklist both with new presentations of the symptom of breathlessness as well as in those with established disease, and we need to bear this list in mind when examining the patient. The patient with COPD might on this occasion be breathless not because of an exacerbation but because they have

Key points

- It is essential to bear in mind that breathlessness can have a variety of causes, not all of which are respiratory.
- Physical examination should follow the taking of the medical history and construction of a list of differential diagnoses, and is an opportunity to confirm normality or discover abnormality.
- Physical examination comprises inspection, palpation, auscultation and percussion.
- The respiratory physician must not forget that disease of other systems may also be the cause of the symptoms and that comorbidity is common.

Table 1. Breathlessness: differential diagnosis according to onset

Onset	Differential diagnosis
Within minutes	Pulmonary embolus Pneumothorax MI Cardiac rhythm disturbance Dissecting aneurysm Acute asthma
Over hours or days	Pneumonia Pleural effusion LVF (LV dysfunction or valve dysfunction or septal rupture post-MI) Asthma Exacerbation of COPD Blood loss Lobar collapse Respiratory muscle weakness (Guillain–Barré syndrome)
Over weeks	Infiltration (malignancy, sarcoidosis, fibrosing alveolitis, extrinsic allergic alveolitis, eosinophilic pneumonia) Respiratory muscle weakness (motor neurone disease) Main airway obstruction Anaemia Valvular dysfunction (SBE)
Over months	Same as for 'Over weeks' plus: Obesity Muscular dystrophy Asbestos-related conditions
Over years	COPD Chest wall deformity Heart valve dysfunction Obesity

MI: myocardial infarction; LVF: left ventricular failure; LV: left ventricular; SBE: subacute bacterial endocarditis.

gone into atrial fibrillation, or the patient with known heart failure may this time be breathless because of a complicating pneumonia.

Asking specifically about the onset of the symptom of breathlessness can be helpful in the differential diagnostic process and this is summarised in table 1.

Cough and breathlessness

A practical approach to the assessment of cough and breathlessness is summarised in figure 1.

Physical examination

In the vast majority of cases, taking the medical history should lead to the construction of a list of differential diagnoses. The examination is then an opportunity either to confirm normality or to discover abnormalities consistent with one or other of one's

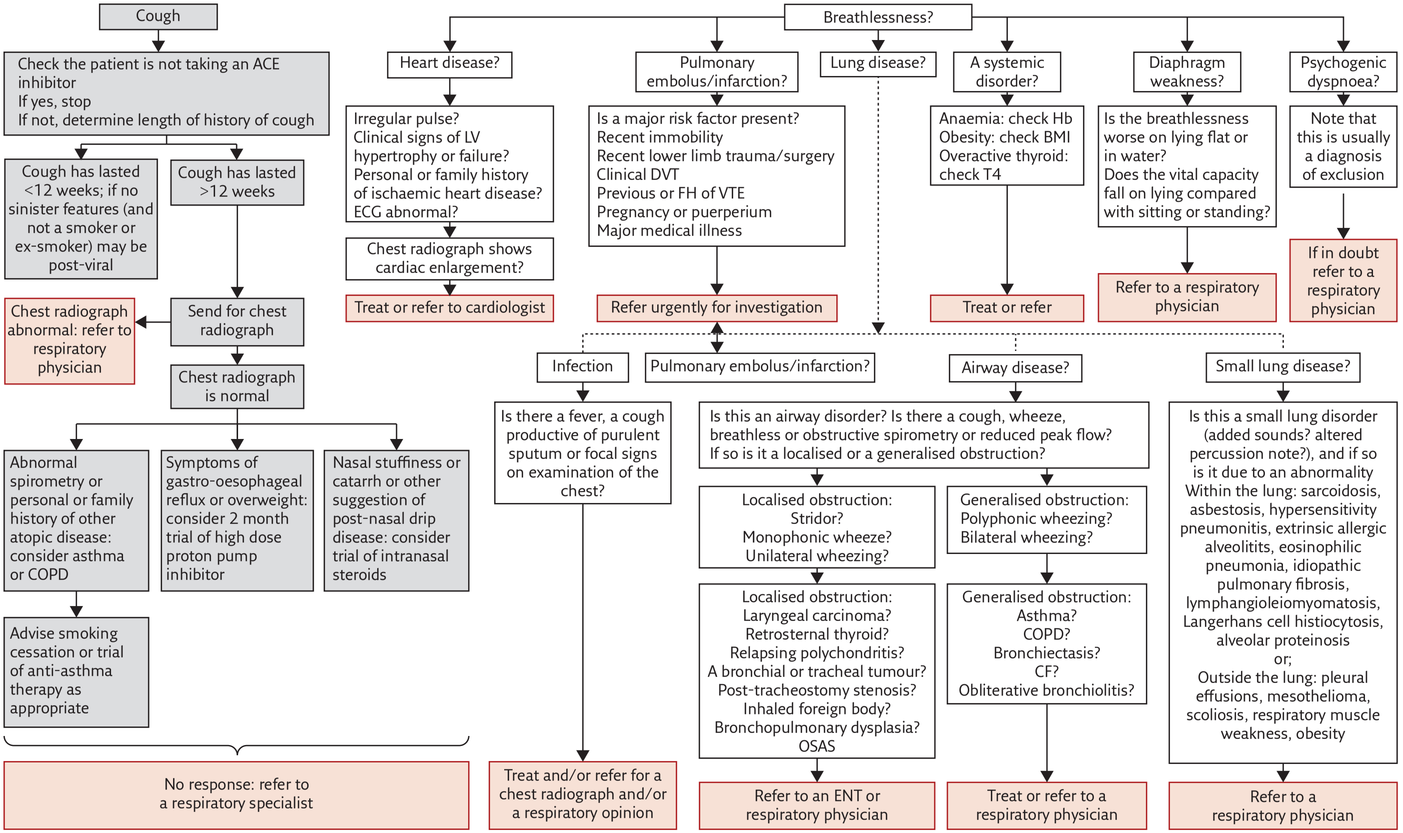

Cough
Check the patient is not taking an ACE inhibitor
If yes, stop
If not, determine length of history of cough
Cough has lasted <12 weeks; if no sinister features (and not a smoker or ex-smoker) may be post-viral
Cough has lasted >12 weeks
Send for chest radiograph
Chest radiograph abnormal: refer to respiratory physician
Chest radiograph is normal
Abnormal spirometry or personal or family history of other atopic disease: consider asthma or COPD
Symptoms of gastro-oesophageal reflux or overweight: consider 2 month trial of high dose proton pump inhibitor
Nasal stuffiness or catarrh or other suggestion of post-nasal drip disease: consider trial of intranasal steroids
Advise smoking cessation or trial of anti-asthma therapy as appropriate
No response: refer to a respiratory specialist
Breathlessness?
Heart disease?
Irregular pulse?
Clinical signs of LV hypertrophy or failure?
Personal or family history of ischaemic heart disease?
ECG abnormal?
Chest radiograph shows cardiac enlargement?
Treat or refer to cardiologist
Pulmonary embolus/infarction?
Is a major risk factor present?
Recent immobility
Recent lower limb trauma/surgery
Clinical DVT
Previous or FH of VTE
Pregnancy or puerperium
Major medical illness
Refer urgently for investigation
Lung disease?
A systemic disorder?
Anaemia: check Hb
Obesity: check BMI
Overactive thyroid: check T4
Treat or refer
Diaphragm weakness?
Is the breathlessness worse on lying flat or in water?
Does the vital capacity fall on lying compared with sitting or standing?
Refer to a respiratory physician
Psychogenic dyspnoea?
Note that this is usually a diagnosis of exclusion
If in doubt refer to a respiratory physician
Infection
Is there a fever, a cough productive of purulent sputum or focal signs on examination of the chest?
Treat and/or refer for a chest radiograph and/or a respiratory opinion
Pulmonary embolus/infarction?
Airway disease?
Is this an airway disorder? Is there a cough, wheeze, breathless or obstructive spirometry or reduced peak flow?
If so is it a localised or a generalised obstruction?
Localised obstruction:
Stridor?
Monophonic wheeze?
Unilateral wheezing?
Localised obstruction:
Laryngeal carcinoma?
Retrosternal thyroid?
Relapsing polychondritis?
A bronchial or tracheal tumour?
Post-tracheostomy stenosis?
Inhaled foreign body?
Bronchopulmonary dysplasia?
OSAS
Refer to an ENT or respiratory physician
Generalised obstruction:
Polyphonic wheezing?
Bilateral wheezing?
Generalised obstruction:
Asthma?
COPD?
Bronchiectasis?
CF?
Obliterative bronchiolitis?
Treat or refer to a respiratory physician
Small lung disease?
Is this a small lung disorder (added sounds? altered percussion note?), and if so is it due to an abnormality
Within the lung: sarcoidosis, asbestosis, hypersensitivity pneumonitis, extrinsic allergic alveolitits, eosinophilic pneumonia, idiopathic pulmonary fibrosis, lymphangioleiomyomatosis, Langerhans cell histiocytosis, alveolar proteinosis
or;
Outside the lung: pleural effusions, mesothelioma, scoliosis, respiratory muscle weakness, obesity
Refer to a respiratory physician

Figure 1. Symptoms and clinical examination in the diagnosis of lung disease. ACE: angiotensin-converting enzyme; LV: left ventricular; DVT: deep vein thrombosis; FH: family history; VTE: venous thromboembolism.

differential diagnoses. Key features, as with all clinical examination, depend upon inspection, palpation, auscultation and percussion.

Inspection

On inspection, the key points to observe are as follows.

- General appearance (breathlessness or cachexia, anaemic?).
- Respiratory rate.
- Cyanosis?
- Appearances of the hand (finger clubbing (figure 2), tremor, tobacco staining or flapping tremor of the outstretched hands suggestive of carbon dioxide retention?).
- Does the chest wall move symmetrically?
- Are there any chest wall deformities (scoliosis or pectus excavatum) or scars (figures 3 and 4)?
- Are there any abnormal vessels suggestive of superior vena cava obstruction (figure 5)?
- Nasal stuffiness or obstruction should be noted.
- A note should be made of the neck/collar size, and also of obvious jaw abnormalities or oropharyngeal abnormalities.
- Examination of the lower limbs with especial reference to signs suggestive of deep venous thrombosis or of skin changes such as erythema nodosum is an essential part of a respiratory examination.

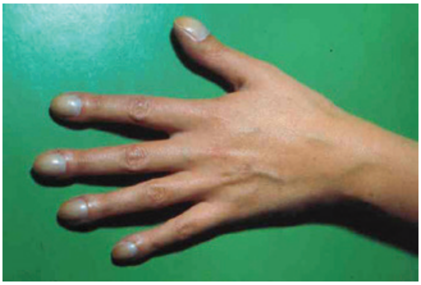


Figure 2. The presence of finger clubbing should be noted and the patient asked if they are aware of how long it has been present or whether a doctor has commented upon it previously.

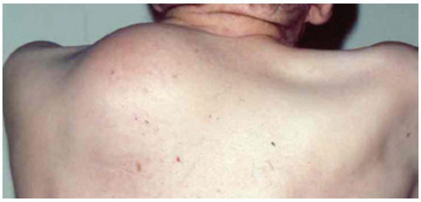


Figure 3. The chest wall should be carefully examined for clues as to underlying lung disease. In this case, an infiltrating lung tumour is invading the chest wall.

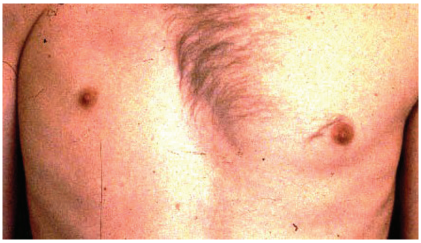


Figure 4. Chest wall abnormalities may be congenital or acquired. In a case of congenital absence of the pectoralis major, as seen here, the abnormality should be noted to avoid potential confusion when interpreting the chest radiograph.

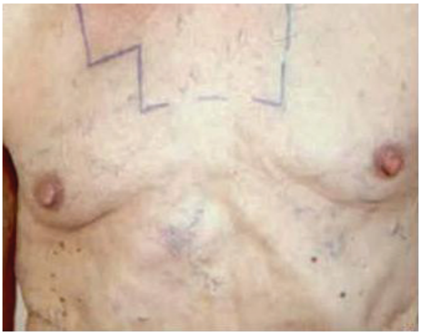


Figure 5. Dilated vessels over the anterior chest wall are often the most obvious sign of superior vena cava obstruction, with the other feature being a raised jugular venous pressure that is non-pulsatile.

Remember that an inspection of relevance to the respiratory system involves more than inspection of the chest itself; for example, one should note erythema nodosum (figure 6) or gynaecomastia (figure 7).

Palpation

This involves the following.

- Assessment of chest expansion, where we may be able identify reduced expansion symmetrically, suggestive of hyperinflation, or reduced movement on one side, suggesting localised pathology on that side.
- Determining the position of the trachea by inserting the index and middle fingers in the suprasternal notch.
- Examining the cervical and supraclavicular lymph nodes for enlargement.
- Assessing the vocal fremitus by asking the patient to loudly and deeply repeat the words ‘ninety-nine’ while you compare both sides of the chest. Voice sounds are better transmitted through consolidated lung than normal lung and poorly transmitted through pleural effusions.

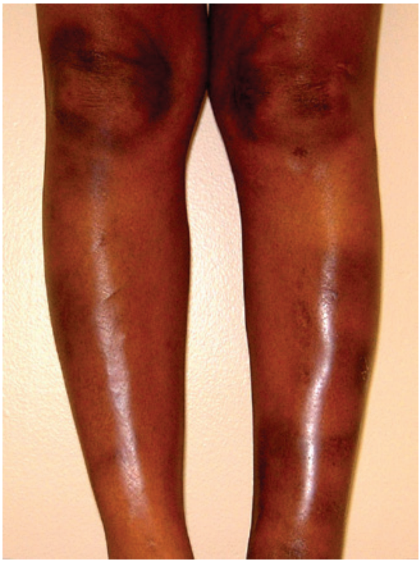


Figure 6. Inspection of the respiratory system involves more than inspection of the chest. In this example, the presence of erythema nodosum is likely to explain the pulmonary abnormalities.

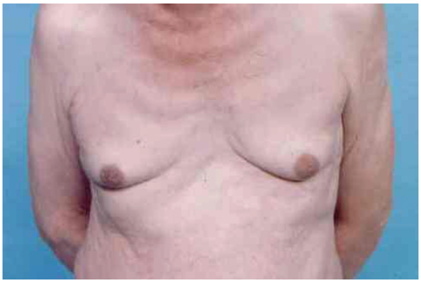


Figure 7. While gynaecomastia can occur for a number of reasons, its presence should always be noted and an important underlying cause to consider is lung cancer.

Percussion

Percussion is often carried out poorly. The key features are to:

- make the movement of your finger a stroke from the wrist;
- strike firmly at right angles upon the finger of the other hand, which lies along the intercostal space; and
- do so in a symmetrical manner, systematically comparing both sides of the chest at a point equidistant from the midline.

The percussion note may be hyper-resonant symmetrically in patients with underlying hyperinflated lungs or asymmetrically in a large pneumothorax, or may be dull in cases of consolidation or pleural effusion.

Auscultation

Listening to the breath sounds involves the following.

- Checking for the presence of bronchial breathing, which is the presence of breath sounds that are similar to those heard over the large central airways in a more peripheral location. Bronchial breathing is classically heard over a consolidated lung (and in association with dullness to percussion), but is also sometimes heard over the upper aspect of a pleural effusion and sometimes over a collapsed lung.
- Determining whether there are any abnormal added sounds, which may be musical sounds (wheezing) or crackles or squeaks. In cases of wheezing, it is important to determine whether the wheezing is polyphonic and bilateral, as in asthma or COPD, or monophonic and localised, as may be found in cases of lung cancer, bronchial stenosis or inhaled foreign bodies.
- Crackles may be fine, and occur in cases of interstitial lung disease or acutely in cases of pulmonary oedema, or coarse, as often heard in patients with bronchiectasis.
- Squeaks are short high-pitched sounds detected in the mid-inspiratory phase due to bronchiolar diseases (chronic hypersensitivity bronchiolitis or bronchiolitis).
- Pleural rubs sound like a squeaky noise, are usually localised and clearly vary in intensity with respiration. Care in interpreting a noise as a pleural rub is necessary in very thin patients, where the diaphragm of the stethoscope may move over the ribs.
- Vocal resonance is found under the same circumstances as vocal fremitus and, when found in conjunction with bronchial breathing, is highly suggestive of consolidation. Some physicians find detection of whispering pectoriloquy a more definite sign; to elicit this, one asks the patient to whisper 'ninety-nine' and, when it is present (such as in cases of consolidation), the whispered sound is heard clearly over the chest wall when transmitted through consolidated lung, whereas a normally air-filled lung would muffle the whispered sound and make it indistinct.

Finally, one should remember that disorders of other systems may coexist and, while examining the chest, one should especially look for evidence of heart and pulmonary vascular disease, noting signs of peripheral oedema and elevation of the jugular venous pressure.

Further reading

- Chapman S, *et al.* (2005). Oxford Handbook of Respiratory Medicine. Oxford, Oxford University Press.
- Partridge MR, ed. (2006). Understanding Respiratory Medicine: a Problem-Oriented Approach. London, Manson Publishing.

Bronchoscopy

Pallav L. Shah

Bronchoscopy is an essential tool for the pulmonologist that allows inspection and sampling of the airways. The technique has evolved in the past decade to also sample structures adjacent to the airways (the tracheobronchial tree). Furthermore, it has evolved to an important therapeutic tool in pulmonology. The procedure is usually performed with or without conscious sedation, with interventional procedures being performed under deep sedation or general anaesthesia.

Equipment

The flexible bronchoscope has evolved from a fibreoptic instrument to videobronchoscopes, which are now almost universally used in most centres (figure 1). The videobronchoscope consists of a video chip at the distal end, an instrument channel and optical fibres that illuminate the airways. The images obtained are then transmitted to a monitor. The distal end of the bronchoscope can be angled through to 180º. This, in combination with manual rotation movements, allows the bronchoscope to be manipulated in the airways.

Indications

Bronchoscopy provides diagnostic information in patients with suspected lung cancer or diffuse lung disease, and in patients with persistent infection or local pulmonary infiltrates (table 1).

Therapeutic bronchoscopy was traditionally performed for malignant disease. However, there are now a number of therapeutic procedures for asthma, COPD and emphysema:

- Clearance of airway secretions
- Removal of foreign bodies
- Palliation of endobronchial airway obstruction by tumour ablation or insertion of stents

Key points

- Bronchoscopy provides diagnostic information in suspected lung cancer and diffuse lung disease, and in patients with persistent infection or local pulmonary infiltrates.
- Bronchoscopy also has therapeutic uses in tumour treatment, and more recently in asthma and emphysema.

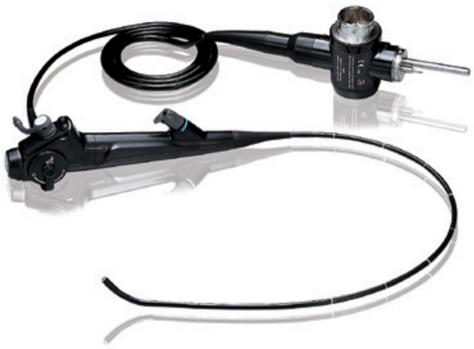


Figure 1. Flexible videobronchoscope (model BF-Q180; Olympus Europa, Hamburg, Germany).

- Flexible microwave ablation of early stage peripheral lung cancers
- Bronchial thermoplasty for asthma
- Bronchoscopic lung volume reduction for emphysema
- Targeted lung denervation for COPD
- Spray cryotherapy treatment with liquid nitrogen for chronic bronchitis

Patient preparation

Patients should be given a full explanation of the procedure accompanied by written information. Below is a simple pre-procedure check list:

- Patient information – verbal and written
- Informed consent

Table 1. Indications for bronchoscopy

Investigation of symptoms
Haemoptysis
Persistent cough
Recurrent infection
Investigation of suspected neoplasia
Unexplained paralysis of vocal cords or hemidiaphragm
Stridor
Localised monophonic wheeze
Suspicious sputum cytology
Unexplained pleural effusions
Mediastinal tissue diagnosis and staging
Assess suitability for surgery
Staging of lung cancer
Assessment of persistent or recurrent infection
Identification of organisms
Evaluate airways
Assessment of diffuse lung disease

- Full blood count and clotting – before transbronchial lung biopsy
- ECG if history of cardiac disease
- Ensure patients do not eat or drink for at least 4–6 h before the procedure
- Ensure patients have someone to take them home following the procedure if they receive sedation
- Patients are advised not to drive or operate machinery for at least 24 h after any sedation

Patients are monitored by continuous oximetry throughout the procedure. Those with pre-existing cardiac disease or hypoxia that is not fully corrected by oxygen therapy should undergo continuous ECG monitoring.

Procedure

The oropharynx is anaesthetised with 4% lidocaine spray and the nasal passage with 2% lidocaine gel. Venous access should always be secured before the procedure and oxygen administered *via* a single nasal cannula. Bronchoscopy can be performed with or without sedation (figure 2). The choice of sedative drugs varies with local practice. Midazolam at a dose of 2–5 mg administered intravenously is more commonly used and has the advantage of amnesic properties in addition to its sedative effect. Alternative or adjunctive agents are opiates, such as fentanyl or alfentanil, which also have antitussive properties. A number of institutions are now switching to nurse-administered sedation and using low-dose propofol infusions as a very short-acting general anaesthetic.

In the nasal approach, the bronchoscope is lubricated with 2% lidocaine gel and passed through the nares under direct vision. It is then inserted into the nasopharynx until the epiglottis is visualised.

In the oral approach, the patient is asked to bite gently onto a mouth-guard; the bronchoscope is then inserted through this mouth-guard into the posterior pharynx, to the level of the epiglottis.

The movement of the vocal cords is assessed and they are then anaesthetised using 2-mL aliquots of 2% lidocaine. When the coughing has subsided, the bronchoscope is advanced through the widest part of the glottis, taking care not to touch the

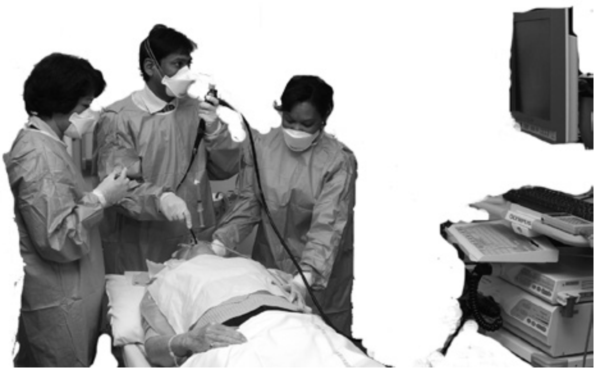


Figure 2. Performance of the bronchoscopy.

vocal cords. The subglottic area of the trachea is very sensitive and patients initially feel as though they are choking. Further 2-mL aliquots of 2% lidocaine are administered in the trachea, carina, and right and left main bronchi. During bronchoscopy, the trachea, bronchi and airways down to the subsegmental level are carefully inspected for the presence of mucosal abnormalities, secretions, anatomical variants, malacia (degree of collapse of trachea and main bronchi in expiration) and endobronchial lesions (figure 3). Narrowing of the bronchial tree as a result of external compression from large lymph nodes or masses is also noted.

Bronchoscopic sampling

Bronchoscopy also provides an opportunity to obtain a variety of samples which may aid diagnosis.

Bronchial washings

The specimens are obtained by injection of 20 mL normal saline into the affected segment of the lung, followed by aspiration.

Bronchial brushings

A fine cytology brush may be used to scrape cells from the surface of any visible lesion or from segments when the lesion is not visible at bronchoscopy. The bronchial brush specimen may be smeared onto a slide and fixed before cytological analysis, or shaken into saline or cytofix for cytospin preparations.

Bronchial biopsy

Any endobronchial abnormalities should be biopsied. At least four samples should be obtained and placed in 10% formol saline solution. The diagnostic yield for polypoid lesions should be high (>90%), but is less for submucosal lesions.

Bronchoalveolar lavage (BAL)

BAL is used in the assessment of diffuse lung disease. The bronchoscope is wedged into the segment of interest and 50–60-mL aliquots of warm saline are injected into

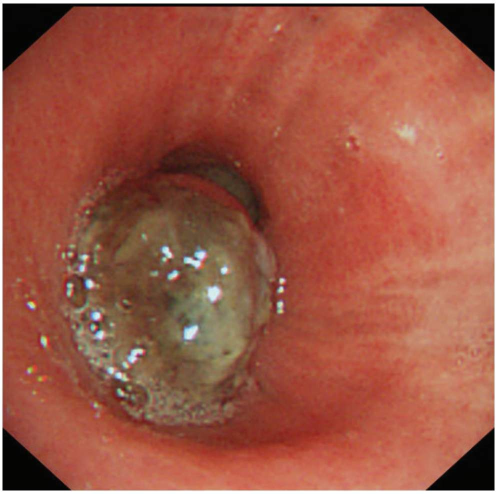


Figure 3. Image obtained through the videobronchoscope.

the segment. The fluid is then slowly aspirated using low-pressure suction or direct hand suction. A total of 150–250 mL is instilled and aspirated.

Transbronchial lung biopsy

Transbronchial lung biopsy is used to obtain parenchymal lung tissue for the evaluation of selected diffuse lung diseases. It is particularly useful when a bronchocentric component is visible on CT scans. The cryo-transbronchial lung biopsy approach is used for other diffuse lung diseases and is discussed later (see the section on cryobiopsy under 'Advanced diagnostic procedures'). The closed biopsy forceps are advanced into a specific bronchial segment until they meet with resistance. The forceps are then withdrawn a short distance and the jaws opened. The patient is asked to take a deep breath and the open forceps are advanced further. When there is further resistance, the patient is asked to breathe out and a biopsy sample is taken during expiration. Samples are obtained from the periphery of the lung.

Transbronchial fine-needle aspiration

Mediastinal and hilar lymph nodes can be sampled by transbronchial fine-needle aspiration (TBNA). The site of aspiration is planned on the basis of a cross-sectional CT. The needle is inserted at the desired point perpendicular to the airway wall. The needle is moved back and forth after penetration of the airway wall and suction applied with a 20-mL syringe. Samples collected can then be used to prepare slides, or be placed in cytofix or saline solution for cytological analysis. This is useful in the staging and diagnosis of suspected lung cancer. This should be performed prior to any other aspects of bronchoscopy so as not to carry over cells from endobronchial lesions into TBNA specimens and, hence, falsely up-stage the patient. Needle aspiration of submucosal lesions may also improve diagnostic yield. Overall, TBNA is a low-risk procedure with a good yield. However, there has been a dramatic shift towards endobronchial ultrasound (EBUS)-guided TBNA in the majority of centres.

Complications

The adverse effects of flexible bronchoscopy may be due to the sedation, the local anaesthesia or the procedure. The overall incidence of complications is ~2%. Mortality from the procedure is <0.02%.

Sedative drugs may depress respiration and have cardiovascular effects (*e.g.* hypotension). Lidocaine may very rarely cause bradycardia, seizures, bronchospasm or laryngeal spasm.

The procedure may cause bronchospasm, laryngospasm, hypoxaemia or cardiac arrhythmias, particularly in patients with pre-existing cardiac disease or hypoxia not corrected by oxygen supplementation. Infection can be introduced by the bronchoscope. Therefore, it is essential to clean and disinfect all instruments before use. Haemorrhage and pneumothorax may follow transbronchial lung biopsy. The risk is 5–7%, and this is increased with paroxysmal coughing. Hypoxia and precipitation of respiratory failure are the main complications of BAL, particularly as the procedure is often performed in patients with diffuse lung disease.

Advanced diagnostic procedures

The airway is illuminated by blue light during fluorescence bronchoscopy. Normal tissue is visible as fluorescent green, whereas abnormal areas appear brown and red in colour. This absence of autofluorescence occurs in dysplasia, carcinoma *in situ* and invasive carcinoma, and may enable the earlier detection of endobronchial tumours.

It is currently used as a research tool, but may also be useful in routine practice. Narrow band imaging emphasises the blood vessels and increased capillary loops in the mucosa, which is associated with dysplasia and carcinoma *in situ*. Magnification of images and presentation at high definition further enhances the ability of the operator to detect subtle abnormalities.

Endobronchial ultrasound

EBUS-guided TBNA is performed with an integrated linear array ultrasound bronchoscope. It provides excellent ultrasound images of the mediastinum and tissue adjacent to the airways, and allows ultrasound-guided sampling of mediastinal lymph nodes or peribronchial tumour masses. The sensitivity of this technique is high and has significantly reduced the need for mediastinoscopy. Its use has rapidly expanded, and it is regarded as the primary step in the diagnosis and staging of lung cancer in the majority of guidelines. It is particularly indicated in:

- Staging and diagnosis of lung cancer
- Sampling para tracheal and para bronchial masses
- Diagnosis of sarcoidosis in the presence of hilar and/or mediastinal adenopathy
- Suspected TB

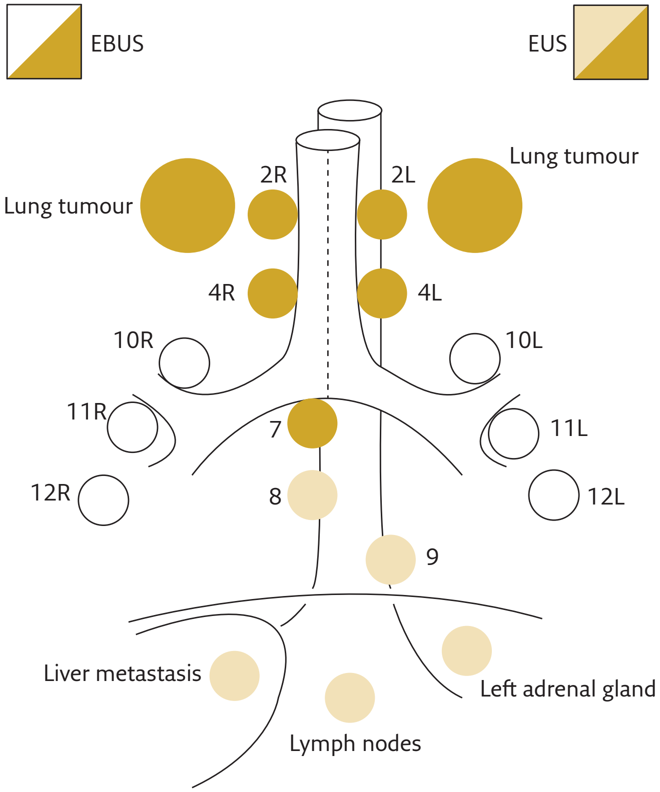


Figure 4. Access of para tracheal and para bronchial structure with the aid of EBUS and EUS. Reproduced from Vilmann et al. *(2015).*

Although beyond the scope of this section, a combined approach of EBUS with endoscopic approach through the oesophagus (EUS(B)) using the same scope has a greater yield than EBUS alone (figure 4).

The role of EBUS in the diagnosis for other diseases, such as sarcoidosis, has also been established in randomised controlled trials. Finally, culture of lymph node aspirates, such as in suspected TB, has a greater yield that simple bronchial lavage.

Radial endobronchial ultrasound

A radial or mini-probe system can be used for localising peripheral pulmonary masses. These probes are passed through the instrument channel of a flexible bronchoscope into the desired segment with a guide sheath. The probe is manipulated in the airways with or without radiological guidance. Once the abnormal area is identified, the sheath is maintained in position, the radial ultrasound probe is removed, and washings, brushings and biopsies obtained *via* the guide sheath.

Cryobiopsy

Cryoprobes may be used to obtain better tissue samples either endobronchially or for transbronchial lung biopsy. Patients need to be intubated with an endotracheal tube or laryngeal mask. The cryoprobe is passed through the instrument channel of the bronchoscope and applied to the tissue to be biopsied. The freezing effects cause the tissue to become adherent and gentle traction is applied to tear off a piece off the frozen tissue. The probe and bronchoscope need to be removed from the airway, and the piece of tissue thawed and placed in formalin. It is not possible to remove the probe through the instrument channel of the bronchoscope when there is tissue adherent to the tip, hence the need to intubate the patient. If transbronchial lung biopsy is performed with cryoprobes, it is essential to use fluoroscopy in order to minimise the risk of a pneumothorax. Furthermore, prophylactic use of adjuncts, such as blocking balloons, is recommended to minimise the risk of bleeding. The balloon should be placed in the segmental orifice where the transbronchial cryobiopsy is being obtained, and inflated immediately after removing the cryoprobe and bronchoscope as one unit. This ensures that the tamponade effect controls any bleeding and importantly reduces the risk of blood overspilling into adjacent airways (the main cause of asphyxia due to endobronchial bleeding). Care is also taken (with fluoroscopic guidance) to obtain the biopsies about 1 cm from the pleural edge to further minimise risk of bleeding and a pneumothorax. More central biopsies, where there are larger vessels, are associated with a greater risk of haemorrhage and more peripheral biopsies with a greater risk of pneumothorax.

Therapeutic procedures

Treatment of endobronchial tumours

The therapeutic role of bronchoscopy is rapidly increasing. It is well established in the treatment of endobronchial tumour obstruction. A variety of techniques, such as cryotherapy, electrocautery or laser, can be utilised by flexible bronchoscopy to rapidly debulk tumours that are obstructing the main airways. Several clinical series have demonstrated that these techniques are very effective in palliating symptoms and improving the quality of life of patients with endobronchial tumour occlusion. They also reduce the risk of post-obstructive pneumonia. Where the airway wall structure has been extensively damaged or there is extrinsic compression from the tumour, endobronchial stents can be used to support the airways. Metal self-expanding stents can be inserted *via* flexible bronchoscopy and are available in both uncovered and covered formats.

Brachytherapy is localised radiotherapy administered to an area of tumour infiltration. A blind-ending catheter is inserted through the instrument channel of the bronchoscope into the desired airway. The bronchoscope is then removed while maintaining the catheter in the appropriate position. The catheter can then subsequently be loaded with a remote device that is used to insert radiotherapy beads and, hence, deliver local radiotherapy. This technique can also be used to treat endobronchial obstruction. However, there is a risk of acute localised oedema following the procedure and treatment carries a significant risk of severe haemorrhage.

Foreign body removal and mucus impaction

Foreign bodies can also be removed using bronchoscopy with tools such as grasping forceps, baskets and in cases where there is food debris with a cryoprobe. Bronchoscopy also has an important role in the intensive care setting, where it can be used to aspirate impacted secretions which impair ventilation in patients on mechanical ventilation. This can be achieved by simple measures such as bronchial lavage and aspiration, or in more difficult cases of mucus impaction by using a cryoprobe. The cryoprobe is placed in the central portion of the impacted bronchus and the probe moved back and forth during the freezing action. The mucus adheres to the probe and can then be removed by pulling out the cryoprobe and bronchoscope together. Care must be taken to keep the probe central to prevent it from sticking to the side of the bronchus.

Bronchoscopic treatment of asthma and COPD

More recently, a number of innovations have been developed for the bronchoscopic treatment of patients with severe emphysema with significant hyperinflation. Endobronchial valves, such as zephyr valves and intrabronchial valves, can be used for bronchoscopic volume reduction. These have been shown to be effective in patients with severe hyperinflation where the target lobe does not have any collateral ventilation. Other developments under evaluation include airway stents, biological polymers, endobronchial coils and thermal vapour. Bronchial thermoplasty, a novel treatment for patients with moderate-to-severe asthma, is also delivered bronchoscopically. A special catheter is used to apply radiofrequency energy to the airways in order to destroy airway smooth muscle. More recently, attention has focused on bronchoscopic treatments for chronic obstructive airways disease with approaches such as targeted lung denervation, metered spray cryotherapy treatment and electroporation.

Further reading

- Bronchoscopy International. www.bronchoscopy.org
- Colella S, *et al.* (2018). Transbronchial lung cryobiopsy in interstitial lung diseases: best practice. *Respiration*; 95: 383–391.
- Interventional Bronchoscopy. www.interventionalbronchoscopy.co.uk
- Shah PL (2011). Atlas of Bronchoscopy. London, Hodder Arnold.
- Shah PL, *et al*. (2017). Lung volume reduction for emphysema. *Lancet Respir Med*; 5: 147–156.
- van Geffen WH, *et al.* (2019). Surgical and endoscopic interventions that reduce lung volume for emphysema: a systemic review and meta-analysis. *Lancet Respir Med*; 7: 313–324.
- Vilmann P, *et al.* (2015). Combined endobronchial and oesophageal endosonography for the diagnosis and staging of lung cancer. *Eur Respir J*; 46: 40–60.

Interventional pulmonology

Hervé Dutau and David Breen

Interventional pulmonology is a well-established subspecialty of respiratory medicine and is becoming increasingly important in the management of both benign and malignant diseases of the lung and pleura. An increasing number of centres in Europe and the USA provide interventional pulmonology services and indeed this subspeciality has become a central component of lung cancer multidisciplinary teams and frequently interacts seamlessly with other specialties including oncology, internal medicine, otorhinolaryngology, thoracic surgery or gastroenterology.

Interventional pulmonology offers cost effective, out-patient and minimally invasive diagnostic (discussed in more detail in the section on Bronchoscopy pp. 124–131) and therapeutic strategies for chest diseases, from prevention to palliative care. Examples of such interventions include: lung cancer diagnosis and staging with minimally invasive approaches such as endobronchial ultrasound (EBUS) and navigation technology; management of complex airway strictures and obstruction with rigid bronchoscopy and airway stenting; management of complex pleural effusions with indwelling pleural catheters and medical thoracoscopy; and endoscopic treatment of emphysema and bronchial asthma. The latter subject is addressed in the section on Bronchoscopy (pp. 124–131).

Main areas of application and future development

Management of central airway obstruction

The endoscopic management of malignant central airway obstruction should only be proposed to symptomatic patients with imminent respiratory failure, stridor

Key points

- Interventional pulmonology offers cost-effective, out-patient and minimally invasive diagnostic and therapeutic strategies for chest diseases, from prevention to palliative care.
- It occupies a central position in the lung cancer multidisciplinary service and frequently interacts seamlessly with other specialties including oncology, internal medicine, otorhinolaryngology, thoracic surgery or gastroenterology.
- Interventional pulmonology has supported many changes in decades-old diagnostic and therapeutic paradigms in pulmonary diseases.
- This has been supported by the rapid progress made in modern medical technologies and by the increase in both the numbers and skillset of interventional pulmonology physicians.

and/or severe dyspnoea. The National Institute for Health and Care Excellence (NICE) guideline for lung cancer published in 2011 recommended that all cancer networks should offer patients rapid access to a team capable of providing interventional endobronchial treatments.

Interventional procedures should be undertaken in patients with a proximal obstruction (trachea, main stem bronchi or bronchus intermedius), with associated functional lung parenchyma distal to the obstruction and in the absence of significant pulmonary artery involvement. In addition, patients should have a predicted adequate life expectancy and performance status post procedure. The endoscopic management consists of mechanical debulking (this is achieved faster and with greater safety with rigid bronchoscopy) assisted with either thermocoagulation, argon plasma or laser coagulation to restore airway patency (figure 1). Alternatively, radiofrequency ablation (electrocautery) and cryoprobe debulking are techniques frequently used to perform a rapid and safe recanalisation, without rigid bronchoscopy. In addition these later techniques are particularly useful for diseases involving the upper lobes.

A stent can be inserted in patients with a persistent lumen obstruction (>50%) and in those cases post failure of first-line chemotherapy with or without radiotherapy, in order to prevent progressive airway compromise. Management of benign central airway obstruction (mainly post-intubation or post-tracheostomy tracheal stenosis) should be reserved for inoperable patients and performed in centres with an expert multidisciplinary team. Airway stenting for a duration of 18 months, with a removable stent (*i.e.* silicone or fully covered self-expendable metallic stents) (figure 2), allows definitive cure in approximately 70% of the cases.

Bronchial stenosis is the most frequent complication involving the anastomosis in lung transplanted patients. Dilatation either with balloon or rigid tubes is the first step in management. Stenting with removable stents is indicated in refractory stenosis after failure of two to three dilatations. Silicone stents, left in place for a mean duration of 9 months and then removed, provide overall success in approximately 70% of cases.

Endoscopic treatment of peripheral malignancies

Surgery is the gold standard for isolated peripheral malignancies without nodal involvement (T1–2N0M0). However, up to 25% of patients are inoperable due to comorbidities, age and/or underlying performance status and require an alternative

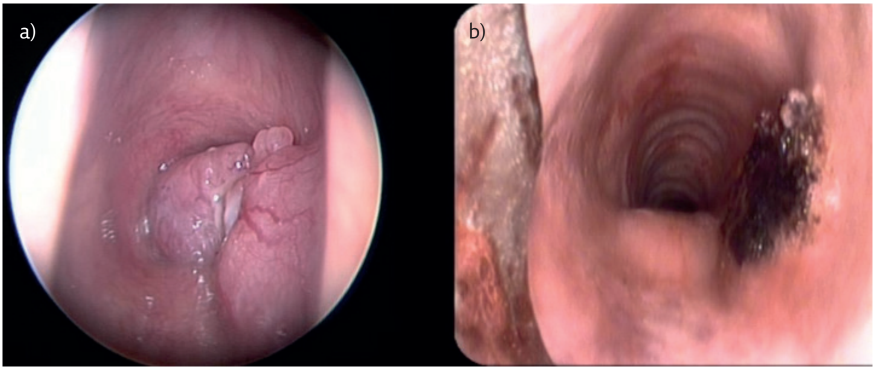


Figure 1. a) Severe obstruction of the upper trachea by an adenoid cystic carcinoma. b) Satisfactory tracheal patency after laser assisted mechanical debulking.

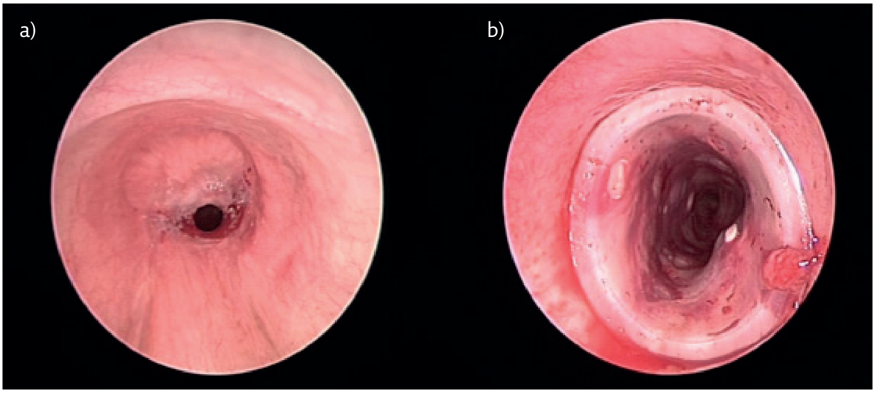


Figure 2. a) Post-tracheostomy tracheal stenosis, and b) after silicone airway stent placement.

management approach (stereotactic radiotherapy, CT-guided transthoracic radiofrequency ablation/microwave or cryotherapy). Trans-thoracic techniques are associated with significant morbidity primarily from the high pneumothorax rate. Recent advances in guided bronchoscopy, including virtual bronchoscopy, ultrathin bronchoscopes, electromagnetic navigation and radial endobronchial ultrasound, has resulted in a greater success for reaching peripheral nodules for histological sampling (figure 3). If these techniques can be further improved it will, in turn, open a potentially new therapeutic approach to the endoscopic minimally invasive treatment of confirmed malignant nodules using varying technologies including radiofrequency, microwave, photodynamic therapy, vapor ablation, cryoablation or direct injection of antimitotic drugs. All these techniques are still investigational at this time and further studies are necessary to evaluate their safety and efficacy.

Management of complex pleural effusions

All units experience a high workload of pleural disease which includes both benign processes such as pneumothorax, pleural space infection and assessment of

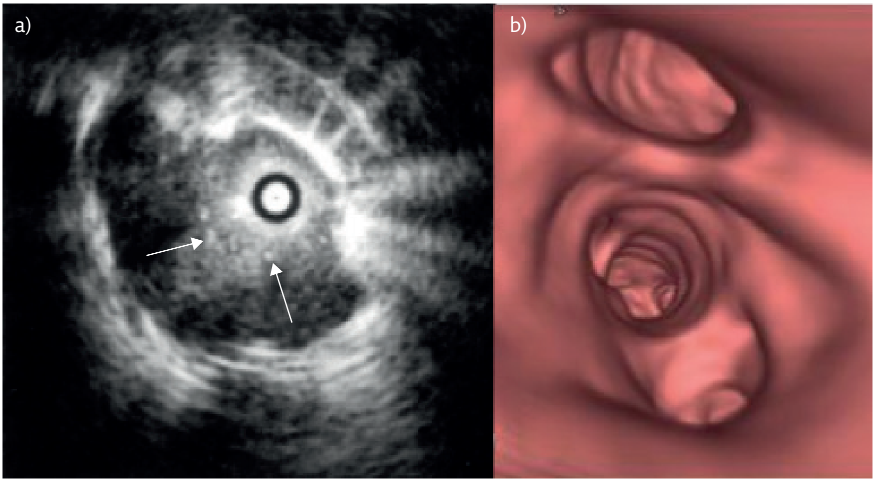


Figure 3. a) Nodule visualised by radial endobronchial ultrasound. b) Image of virtual bronchoscopy.

exudative effusions and malignant diseases, either primary or secondary malignancies of the pleura. Once again ultrasound has become central in the assessment of all pleural diseases. Recently new technologies have allowed less invasive and ambulatory procedures in the most cost-effective setting. The diagnostic assessment and therapeutic management of the pleura utilises older techniques such as medical thoracoscopy with either rigid or semi-rigid instruments and image-guided closed pleural biopsy, and have added new procedures and technologies to the armamentarium of pleural investigations for example, indwelling pleural catheters, pleural manometry and point-of-care thoracic ultrasound.

Undiagnosed exudative pleural effusion should be further assessed by medical thoracoscopy. This allows for pleural biopsies with a high rate of diagnostic accuracy and, in addition, offer an excellent therapeutic option for the management of the malignant pleural space with talc poudrage (figure 4). More recently, indwelling pleural catheters offer a further option for the management of recurrent effusions; offering patients an ambulatory approach to pleural drainage. They are most often indicated for symptomatic patients with short life expectancy (<3 months).

Endoscopic treatment of emphysema

Significant advances have occurred in the endoscopic treatment of emphysema culminating in the publication of updated National Institute for Health and Care Excellence and COPD Global Initiative for Obstructive Lund Disease recommendations in 2017. These guidelines now support the use of endobronchial valve insertion, with adequate safety and efficacy in patients with emphysema. The best evidence is for patients with heterogeneous emphysema and lack of collateral ventilation in the target lobe. Decision on treatment selection and procedures should be performed in centres with expertise and with a dedicated multidisciplinary team. All patients should undergo pulmonary rehabilitation prior to valve insertion. Known complications of valve insertion (figure 5a) include pneumothorax in up to 25% of cases, exacerbation of pre-existing obstructive lung disease, haemoptysis, valve

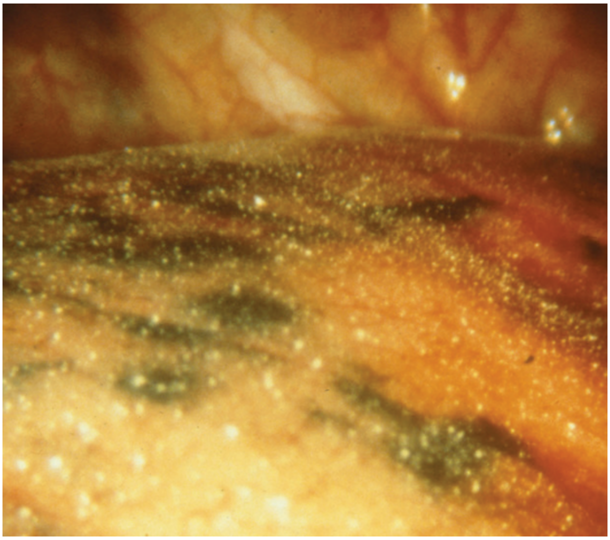


Figure 4. Talc poudrage at the surface of a lung during medical thoracoscopy.

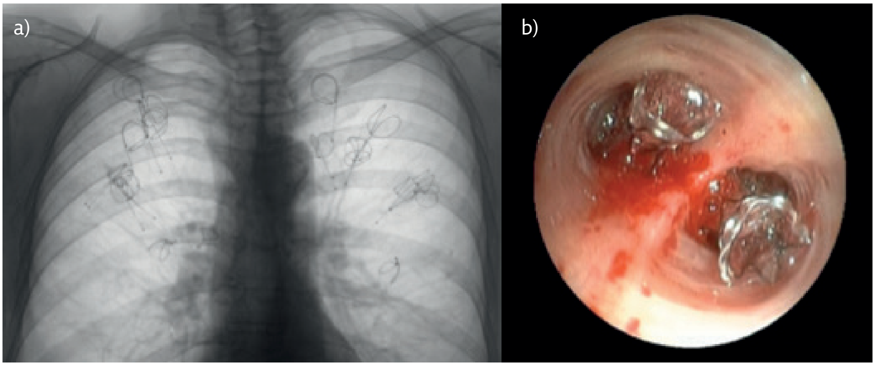


Figure 5. Endoscopic treatment of emphysema. a) Bilateral coil placement in both upper lobes and b) one-way valves inserted in segmental bronchi.

migration and loss of efficacy over time. Other techniques under investigation for emphysema management but not currently recommended outside a clinical trial setting include endobronchial coil insertion (figure 5b), vapour ablation and sealant technology. In addition, techniques are also under investigation for chronic bronchitis and include liquid nitrogen cryospray and denervation technologies.

Conclusion

The field of interventional pulmonology is rapidly developing with a resurgence in older techniques such as rigid bronchoscopy, thoracoscopy and (image-guided) pleural biopsy. In addition, there has been a significant investment in technologies for guidance to peripheral nodules and a major investment by medical device companies in new technologies for the assessment and management of benign diseases of the respiratory system. This resurgence has been supported by various national and international guidelines and recommendations and by the rapid growth of interventional pulmonology fellowships in Europe and the USA.

Recent exciting advances include bronchoscopic ablative therapies utilising navigation technology and manually created tunnels through the lung parenchyma, such as: bronchoscopic transparenchymal nodule access; motorised devices allowing multiple instruments to operate simultaneously in the airways; bronchoscopes with multiple working channels; and steerable and trackable instruments. Further major advances are expected with robotic technology and it's adaptation to bronchoscopy.

A modern interventional pulmonology service occupies a central position in a modern oncology service, both thoracic and non-thoracic. In addition, interventional pulmonology is becoming increasingly important in many benign respiratory diseases. Interventional pulmonology has supported changes in many decades-old diagnostic and therapeutic paradigms in pulmonary diseases. This has been made possible by the rapid progress in modern technologies and by the increase in the numbers and skillsets of interventional pulmonology physicians. In turn, this offers the chance to revolutionise the field of pulmonary medicine in the coming decades. Interventional pulmonology is no longer a dying field of pulmonary medicine but instead has become one of the most rapidly growing subspecialties in modern day medicine.

Further reading

- Bhatnagar R, *et al.* (2016). Advanced medical interventions in pleural disease. *Eur Respir Rev*; 25: 199–213.
- David WH, *et al.* (2018). Bronchoscopic therapies for peripheral lung malignancies. *Clin Chest Med*; 39: 245–259.
- Dooms C, *et al.* (2017). Central airway obstruction. *In*: Herth FJF, *et al.*, eds. Interventional Pulmonology. ERS monograph. Sheffield, European Respiratory Society; pp. 224–235.
- Dutau H, *et al.* (2010). A retrospective study of silicone stent placement for management of anastomotic airway complications in lung transplant recipients: short- and long-term outcomes. *J Heart Lung Transplant*; 29: 658–664.
- Galluccio G, *et al.* (2009). Interventional endoscopy in the management of benign tracheal stenoses: definitive treatment at long-term follow-up. *Eur J Cardiothorac Surg*; 35: 429–433.
- Crespo MM, *et al.* (2018). ISHLT Consensus Statement on adult and pediatric airway complications after lung transplantation: definitions, grading system, and therapeutics. *J Heart Lung Transplant*; 37: 548–563.
- Rami-Porta R, *et al.* (2018). Lung cancer staging: a concise update. *Eur Respir J*; 51: 1800190.
- Slebos DJ, *et al.* (2017). Bronchoscopic lung volume reduction. *In*: Herth FJF, *et al.*, eds. Interventional Pulmonology. ERS monograph. Sheffield, European Respiratory Society; pp. 276–293.

Bronchoalveolar lavage

Ulrich Costabel, Francesco Bonella and Josune Guzman

Bronchoalveolar lavage (BAL) has gained widespread acceptance as a powerful investigative tool in pulmonary medicine and has become a standard diagnostic procedure in patients with interstitial lung diseases (ILDs). BAL is regarded as providing complementary information to histopathology from biopsies, but nevertheless has several advantages over biopsy procedures. It is safer and associated with virtually no morbidity. BAL collects samples from a much larger area of the lungs than can be obtained by the small tissue fragments of transbronchial biopsy or even by surgical biopsy specimen, therefore giving a more representative view of inflammatory and immunological changes.

BAL procedure

BAL is a minimally invasive technique used to obtain cells, inhaled particles, infectious organisms and solutes from the lower respiratory tract and, in particular, from the alveolar spaces of the lung. To achieve this:

- a sufficient volume of lavage fluid must be instilled, which in adults is a minimum of 100 mL; and
- the correct position of the bronchoscope (wedge position) in a segmental or subsegmental bronchus is required.

Guidelines and recommendations for a standardised approach to the performance of BAL, the laboratory processing and the analysis of recovered fluid have been published.

Key points

- Bronchoalveolar lavage (BAL) is a technique to collect cells, inhaled particles, infectious organisms and solutes from the lower respiratory tract and, in particular, from the alveolar spaces of the lung.
- BAL has become a crucial tool in the clinical diagnosis of interstitial lung diseases (ILDs) or lower respiratory tract infections.
- BAL findings must be interpreted in the context of clinical and radiological information.
- BAL can replace lung biopsy in some rare ILDs, such as alveolar proteinosis, Langerhans cell histiocytosis or diffuse alveolar haemorrhage; in other ILDs, BAL can be used to narrow the range of the differential diagnosis or to exclude certain diseases.

When the guidelines are followed, the results of BAL are sufficient for practical diagnostic purposes.

BAL is usually performed during fibreoptic bronchoscopy with topical anaesthesia. To avoid coughing topical anaesthesia must be adequate, and any excess should be removed prior to lavage. BAL can also be carried out under general anaesthesia and in ventilated patients through a rigid bronchoscope or an endotracheal tube. The fibreoptic bronchoscope is gently introduced until impacted, or 'wedged', in a segmental or subsegmental bronchus. The recommended standard site is the right middle lobe or, if this is not accessible, the left lingular lobe in diffuse lung disease, but the area of the greatest radiographic abnormality in localised disease.

Next, sterile, unbuffered isotonic saline (0.9% NaCl solution) pre-warmed to body temperature is instilled with syringes through the biopsy channel of the bronchoscope, using multiple aliquots of 20–60 mL (usually four to five aliquots), up to a total volume of 100–240 mL. Smaller instilled volumes (<100 mL) increase the likelihood of contamination of the lavage fluid by the bronchial spaces, including inflammatory cells from this compartment, which may skew the differential cell counts.

After each instillation, the fluid is immediately recovered by gentle hand suction into the syringe or gentle wall suction into a fluid trap. Suction that is too strong can cause collapse of the distal airways or trauma to the airway mucosa, which reduces the recovery or changes the BAL fluid profile. The airway collapse can be visually controlled by the bronchoscopist. Usually, 40–70% of the instilled volume is recovered. The total volume retrieved should be greater than 30% of the instilled volume to avoid a misleading differential cell count.

Siliconised or plastic containers must be used for collection and processing of BAL fluid to avoid loss of cells through adhesion to glass surfaces. If biopsies are needed, these should be performed after BAL to avoid contamination of BAL with blood.

BAL is generally well tolerated. Side-effects are more or less the same as those of routine fibreoptic bronchoscopy under local anaesthesia except for an increased risk of minor post-BAL fever, which can be minimised by keeping the total BAL instillation volume below 150 mL, and a transient decrease in lung function parameters, both of which are self-limiting and resolve within 24 h. There is practically no mortality, and the complication rate is low, 0–2.3% compared with 7% for transbronchial biopsy and 13% for surgical lung biopsy. There are no absolute contraindications for performance of BAL beyond those noted for bronchoscopy.

Risk factors for developing side-effects are:

- P_{aO_2} <8.0 kPa (<60 mmHg), oxygen saturation below 90%,
- FEV_1 below 1.0 L,
- prothrombin time <50 s, platelet count <20000 mL^{-1},
- significant comorbidity, and
- bronchial hyperreactivity.

Laboratory processing

It is essential that BAL processing is done by clinical and laboratory personnel who are highly trained in the laboratory techniques and their applications and interpretation. The total fluid recovered should be transported to the laboratory as quickly as possible (in <1 hour if kept at room temperature), because the cells are not well preserved in the saline solution. The fluid should be pooled into a single container and the total volume should be measured. The lavage fluid frequently contains large amounts of mucus; therefore, filtration through cotton gauze or nylon mesh is often performed. Filtration leads to a preferential loss of bronchial epithelial cells without a significant effect on the total cell count and cell differentials. After filtration, the fluid is centrifuged for 10 min at 500 $\times g$. The supernatant can be stored frozen at -20°C or -70°C for subsequent analysis of soluble components.

The total number of cells is counted in a haemocytometer, either in a sample of the pooled native fluid or in a resuspension of the cells after the first centrifugation. Washing procedures result in a loss of total cells, but lead to an increase in cell viability of the remaining cells. The total cell count is usually expressed as the total number of cells recovered per lavage and also as the concentration of cells per mL of recovered fluid. Cell viability is assessed by trypan blue exclusion and should range from 80 to 95%

For the enumeration of cell differentials, at least 600 cells are counted on cytocentrifuge or cell smear preparations after staining with May–Grünwald–Giemsa (MGG) stain. This number of cells is needed to achieve sufficient reproducibility and low variability in the differential cell counts. The diff-quick stain should not be used because it does not stain mast cells. Ciliated or squamous epithelial cells should be noted, but not included in the differential cell count. A high percentage of epithelial cells (>5%) is indicative of contamination of the alveolar samples by bronchial cells. Such BAL probes may not be representative for the diagnosis of diffuse parenchymal lung disease. At least three unstained slides should be stored so that special stains (iron, periodic acid–Schiff (PAS), silver, toluidine blue, fat or Ziehl–Neelsen) can be performed if clinically indicated or as arising from specific morphological observations on the MGG slides. Such morphological abnormalities, which should be routinely looked for, include foamy macrophages, giant cells, macrophages containing smoking-related particles, macrophages laden with haemosiderin confirmed by iron staining, inorganic dust particles or fibres, globules of lipoprotein, malignant cells or microorganisms.

To document asbestos exposure, quantitative determination of asbestos bodies can be made after vacuum filtration of the native BAL fluid through a 0.45–1.20 µm Millipore membrane. The exact dust composition can be determined by electron microscopy with energy dispersive X-ray spectroscopy.

Lymphocyte subpopulations can be identified by immunocytochemical methods, immunofluorescence, or flow cytometry using monoclonal antibody techniques. CD1a or Langerin are very specific markers for Langerhans cell histiocytosis. Flow cytometry is also a useful tool to detect markers of malignant lymphoma.

A number of soluble components have been measured in BAL fluid. None of them has proven to be useful in clinical settings.

Normal BAL cytology in healthy adults

The BAL fluid obtained from healthy, nonsmoking adults without lung disease contains only small percentages of lymphocytes, neutrophils and other inflammatory cells. Alveolar macrophages are the predominant cell population. Published normal ranges for BAL from the standard site (the right middle lobe) show considerable variability when expressed per mL or absolute total numbers. However, results are very similar when expressed as differential percentage counts, consistent with these not being influenced by dilution. The normal ranges for differential cell counts in healthy nonsmokers are:

- macrophages >80%
- lymphocytes ≤15%
- neutrophils ≤3%
- eosinophils ≤0.5%
- mast cells ≤0.5%
- plasma cells 0%

Cigarette smoking is a strong confounding factor with significant effects on BAL samples. The alveolar macrophages from smokers are much larger than those in nonsmokers and contain cytoplasmic inclusion bodies (smoker's inclusion bodies). On gross examination, the recovered BAL fluid has a light to dark brown and turbid appearance caused by the colour of the tar-laden macrophages. The total cell yield is three- to five-fold higher in smokers, due to a three- to five-fold numerical increase in the number of macrophages, leading to a relative decrease in the percentage of lymphocytes.

BAL as a clinical diagnostic tool

BAL is broadly indicated in every patient with unclear ILD or unclear pulmonary shadowing, no matter what cause is suspected. BAL may also be indicated in patients with normal chest radiographs when clinical and lung function tests are abnormal and point toward a diffuse lung disease, or in patients with unexplained pulmonary symptoms in whom a normal BAL finding may allow the exclusion of significant, active ILD. Certain HRCT patterns are often considered to be sufficiently diagnostic to avoid

Table 1. Diagnostic BAL findings

BAL finding	Diagnosis
***Pneumocystis jirovecii*, fungi, cytomegalovirus transformed cells**	Opportunistic infections
Milky effluent, PAS-positive noncellular corpuscles, amorphous debris, foamy macrophages	Alveolar proteinosis
Haemosiderin-laden macrophages, intracytosplasmic fragments of red blood cells in macrophages, free red blood cells	Alveolar haemorrhage syndrome
Malignant cells of solid tumours, lymphoma, leukaemia	Malignant infiltrates
Dust particles in macrophages, quantifying asbestos bodies	Dust exposure
Eosinophils >25%	Eosinophilic lung disease
Positive lymphocyte transformation test to beryllium	Chronic beryllium disease
CD1-positive Langerhans cells increased	Langerhans cell histiocytosis
Atypical hyperplastic type II pneumocytes	Diffuse alveolar damage, drug toxicity

Table 2. BAL cellular patterns as an adjunct to diagnosis

Lymphocytic	EAA Chronic beryllium disease Sarcoidosis TB NSIP (mainly cellular type) Lymphocytic interstitial pneumonia Connective-tissue disorders Drug-induced pneumonitis Malignant infiltrates Silicosis Crohn's disease Primary biliary cholangitis HIV infection Viral pneumonia
Neutrophilic (± eosinophilic)	IPF Desquamative interstitial pneumonia Fibrotic NSIP Acute interstitial pneumonia Acute respiratory distress syndrome Bacterial pneumonia Connective tissue disorders Asbestosis Granulomatosis with polyangiitis Diffuse panbronchiolitis Transplant bronchiolitis obliterans Idiopathic bronchiolitis obliterans Drug-induced reaction
Eosinophilic	Eosinophilic pneumonia Eosinophilic granulomatosis with polyangiitis Hypereosinophilic syndrome Allergic bronchopulmonary aspergillosis Desquamative interstitial pneumonia Drug-induced reaction
Mixed cellularity	COP Connective-tissue disorders NSIP Drug-induced reaction Inorganic dust disease

NSIP: nonspecific interstitial pneumonia; IPF: idiopathic pulmonary fibrosis; COP: cryptogenic organising pneumonia. Reproduced and modified from Bonella *et al*. (2010).

Table 3. BAL CD4/CD8 ratio in diseases with a lymphocytic pattern

CD4/CD8 increased	CD4/CD8 normal	CD4/CD8 decreased
Sarcoidosis	TB	EAA
Chronic beryllium disease	Lymphangitic carcinomatosis	Drug-induced pneumonitis
Asbestos-induced alveolitis		COP
Alveolar proteinosis		Silicosis
Crohn's disease		HIV infection
Connective-tissue disorders		

the need for BAL or lung biopsy. However, BAL is always indicated when the clinical investigations plus HRCT fail to establish a confident multidisciplinary diagnosis, or when additional information is needed to confirm, strengthen or exclude a diagnosis. BAL should never be considered as a stand-alone diagnostic test, but should be interpreted in the context of clinical, laboratory and radiographic HRCT findings.

BAL findings may, on occasion, be very specific, so that they can directly confirm a particular diagnosis and can then replace lung biopsy (table 1). It is of interest to note that many of these disorders are included in the group of alveolar filling syndromes. Obviously, the abnormal material which accumulates in the alveolar spaces in these syndromes can easily be washed out by lavage and is so characteristic that a specific BAL diagnosis is possible.

Table 4. Diagnostic yield of BAL in ILD

BAL without biopsy usually sufficient (high sensitivity and high specificity)	Alveolar proteinosis *Pneumocystis* pneumonia Bronchoalveolar carcinoma Malignant non-Hodgkin lymphoma Alveolar haemorrhage Eosinophilic pneumonia
BAL in combination with clinical and HRCT features frequently sufficient (high sensitivity, low specificity)	IPF (neutrophils ± eosinophils) EAA (lymphocytes, plasma cells, foamy macrophages) RB-ILD (smokers' macrophages) COP (mixed cellularity, decreased CD4/CD8 ratio) Lymphangioleiomyomatosis (alveolar haemorrhage)
BAL typical in only 50% of patients, biopsy often needed (if CT atypical) (moderate sensitivity, high specificity)	Sarcoidosis (increased CD4/CD8 ratio) Langerhans cell histiocytosis (CD1a >3%)
BAL mostly not diagnostic, biopsy required (low sensitivity ± low specificity)	Hodgkin disease Invasive aspergillosis

RB-ILD: respiratory bronchiolitis-associated interstitial lung disease. Reproduced and modified from Bonella *et al*. (2010).

In other selected lung diseases, BAL findings are not diagnostic, but may help narrow the differential diagnosis in the appropriate clinical setting and serve as an adjunct to the diagnosis. The list of diseases with a lymphocytic, neutrophilic, eosinophilic or a mixed cellular pattern is long (table 2). Diseases with an increase in lymphocytes can be further differentiated into those with an elevated, normal or decreased CD4/CD8 ratio (table 3). However, the importance of the CD4/CD8 ratio of BAL lymphocytes has been debated because of the high variability in several diseases. Only 50–60% of sarcoidosis patients show an increased CD4/CD8 ratio, and in 15% the ratio is even decreased. In extrinsic allergic alveolitis (EAA), the ratio is not always decreased, as was seen in early BAL studies, but may also be normal or increased.

Some of the ILDs almost always show an abnormal BAL (high sensitivity), although the specificity is low; however, in combination with clinical and HRCT features, diagnosis may be possible without a biopsy (table 4). For example, if the HRCT scan shows a patchy ground-glass pattern, BAL may be able to reveal that this patient suffers from EAA (high lymphocyte count), a smoking-related respiratory bronchiolitis/ILD (high smoker's macrophage count and normal cell differential), or alveolar haemorrhage (high count of haemosiderin-laden macrophages). In a patient with a usual interstitial pneumonia pattern on HRCT suspected of having IPF, a BAL lymphocytosis of >30% would not be compatible with IPF but rather suggestive of chronic EAA. In a patient with predominantly consolidation plus some ground-glass opacities on HRCT, BAL may be suggestive of organising pneumonia (mixed cellular pattern with a relatively low eosinophil count), chronic eosinophilic pneumonia (major increase in eosinophils), bronchoalveolar carcinoma (malignant cells of adenocarcinoma), or malignant lymphoma (monoclonal B-cell population). In drug-induced lung diseases, BAL findings are not specific but can contribute to the expected clinicopathological pattern of a given drug-induced lung disease and can help to exclude other conditions such as infection or lung involvement by the underlying disease. Sometimes, even a normal lavage may be useful to exclude some disorders with a high probability (*e.g.* EAA, eosinophilic pneumonia, alveolar haemorrhage) and to focus attention on another direction.

Further reading

- Bonella F, *et al.* (2010). Bronchoalveolar lavage. *In:* Strausz J, *et al.*, eds. Interventional Pulmonology (ERS Monograph). Sheffield, European Respiratory Society; pp. 59–72.
- Costabel U, *et al.* (2004). Bronchoalveolar lavage in drug-induced lung disease. *Clin Chest Med*; 25: 25–35.
- Costabel U, *et al.* (2011). Bronchoalveolar lavage. *In*: Schwarz MI, King TE, eds. Interstitial Lung Disease. 5th edn. Shelton, People's Medical Publishing House; pp. 149–170.
- Costabel U. (1998). Atlas of Bronchoalveolar Lavage. London, Chapman and Hall.
- Haslam PL, *et al.* (1999). Report of ERS Task Force: guidelines for measurement of acellular components and standardization of BAL. *Eur Respir J*; 14: 245–248.
- Klech H, *et al.* (1989). Technical recommendations and guidelines for bronchoalveolar lavage (BAL). Report of the European Society of Pneumology Task Group. *Eur Respir J*; 2: 561–585.
- Klech H, *et al.* (1990). Clinical guidelines and indications for bronchoalveolar lavage (BAL): report of the European Society of Pneumology Task Force on BAL. *Eur Respir J*; 3: 937–974.
- Meyer KC, *et al.* (2012). An official ATS clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med*; 185: 1004–1014.

Medical thoracoscopy/ pleuroscopy

Philippe Astoul

Background and definition

The increased incidence of pleural-related disease has added a significant workload for pulmonologists, and medical thoracoscopy/pleuroscopy (MT/P) has become the cornerstone investigation of the pleura. Indeed, this ‘open window on the pleural space’ allows accurate diagnosis, staging of pleural cancers and, in many cases, therapeutic options. It is now accepted that this procedure is an integral component of and best practice in the workup of pleural pathology. In the setting of diagnostic and therapeutic chest procedures, a distinction must be made between thoracoscopy performed by pulmonologists (MT/P), which may be video-assisted, and surgical thoracoscopy or video-assisted thoracoscopy surgery (VATS). MT/P is usually performed by pulmonologists in the endoscopy suite under local anaesthesia and with intravenous conscious sedation/analgesia or mild anaesthesia with a patient in spontaneous breathing, while VATS requires general anaesthesia and double-lumen tracheal intubation; it is usually undertaken by thoracic surgeons in the operating theatre. The range of indications and interventions performed differ between the two procedures. MT/P is frequently indicated for diagnostic purposes (pleural effusions) and/or talc pleurodesis (poudrage) to prevent recurrence of a persistent pleural effusions or pneumothorax. To summarise, in all cases where a chest tube is

Key points

- Medical thoracoscopy/pleuroscopy (MT/P) is a minimally invasive procedure and the cornerstone investigation for the pleural diseases, allowing accurate diagnosis and therapeutic options, particularly pleural symphysis.
- In all cases where a chest tube is required, it should take a pulmonologist only a few additional minutes to introduce a rigid or semirigid endoscope into the pleural cavity *via* the same incision to inspect the pleura, to locate any adhesions, to obtain pleural samples and to verify that the chest tube is well positioned.
- Complications of MT/P are very rare and can be easily prevented by a strict pre-operative work-up of the patient. Pre-thoracoscopy evaluation of the chest by chest ultrasonography decreases dramatically the number of futile procedures and allows the identification of a safe trocar entry site.
- Due to the increased incidence of pleural-related disease, MT/P must be included in the training programmes of pulmonologists.

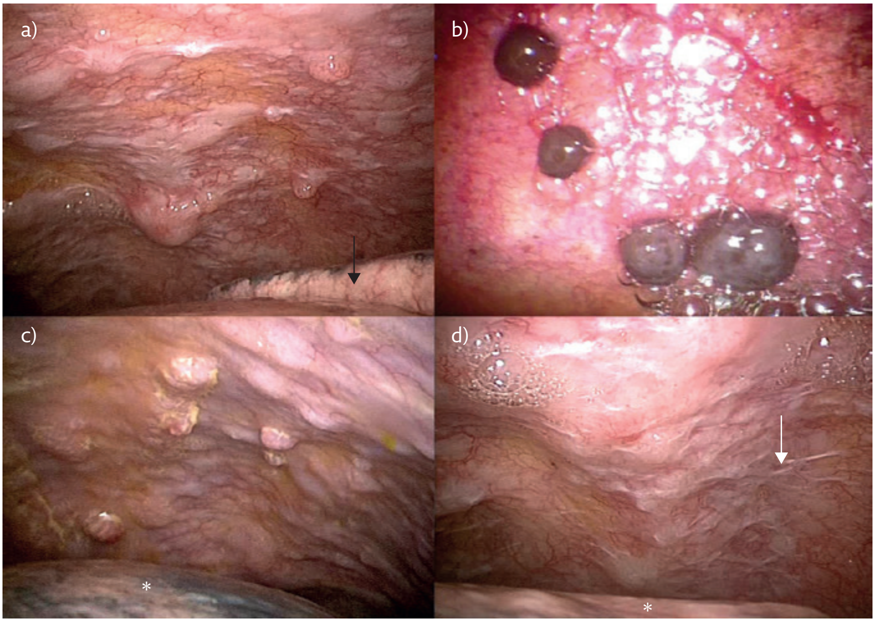


*Figure 1. Endoscopic aspects of pleural cancers. a) Pleural adenocarcinoma. Nodules are visible on the surface of parietal pleura. Arrow: fissure. b) Metastatic nodules of melanoma on the parietal pleura. c) Malignant pleural mesothelioma with nodules. d) Malignant pleural mesothelioma. Flat nodules with neoplastic lymphangitis (arrow). *: lung.*

required, it should take a pulmonologist only a few additional minutes to introduce an endoscope *via* the same incision to inspect the pleural cavity (figures 1 and 2), to locate any adhesions (figure 3), to obtain pleural samples, to insufflate agents for pleural symphysis and to verify that the chest tube is well positioned. Therefore, MT/P is recommended as the method of choice to investigate unexplained exudative pleural effusions after nondiagnostic pleural fluid analysis, allowing pleural biopsies under direct visualisation and associated with a diagnostic yield approaching that of surgical approaches. In addition, treatment of recurrent pleural effusions can be performed in the same setting, *via* pleurodesis or insertion of an indwelling pleural catheter. If MT/P for the diagnosis of exudative pleural effusion and the treatment of recurrent malignant pleural effusion and recurrent spontaneous pneumothorax mainly by pulverisation of dedicated calibrated talc represent a 'green zone' for this procedure, several advanced indications have also been proposed, such as treatment of pleural space infections (grey zone) and lung biopsies (red zone).

Technique

MT/P is a minimally invasive procedure. However, a pre-operative work-up is necessary including the patient's detailed medical history with a medication list (anticoagulants or antiplatelet agents), a complete physical examination, a basic laboratory work-up with coagulation tests, and a careful review of the chest imaging. Physicians should try to balance the benefits with the risks of the procedure. As with all interventions, the procedure should not be performed unless there is a definite benefit to the patient. In the last decade, chest ultrasonography has gained popularity as an efficient technique to analyse pulmonary and pleural structure for the investigation of pleural diseases and the assessment of pleural procedures. Chest ultrasonography is recommended

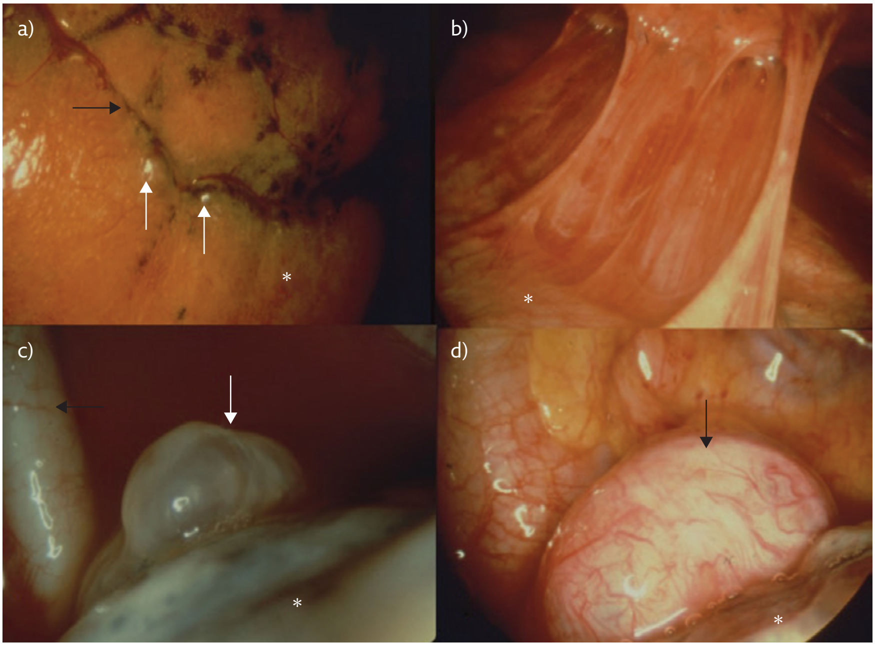


*Figure 2. Endoscopic aspects of pneumothorax. a) Small blebs (white arrows) are visible close to the fissure (black arrow). b) Vascularised adhesion between lung (*) and parietal pleura. c) Apical bleb (white arrow) close to the subclavian artery (black arrow). d) Emphysematous bullae with vascularised surface. *: lung.*

before the MT/P procedure to check the presence of pleural adhesion (figure 3), in order to facilitate the identification of the trocar entry site, and to carefully analyse the chest wall and the pleural cavity (figure 4). Pulse oximetry, noninvasive blood pressure measurements and ECG tracing should be monitored continuously throughout the procedure. The patient is placed in the lateral decubitus position with the healthy lung

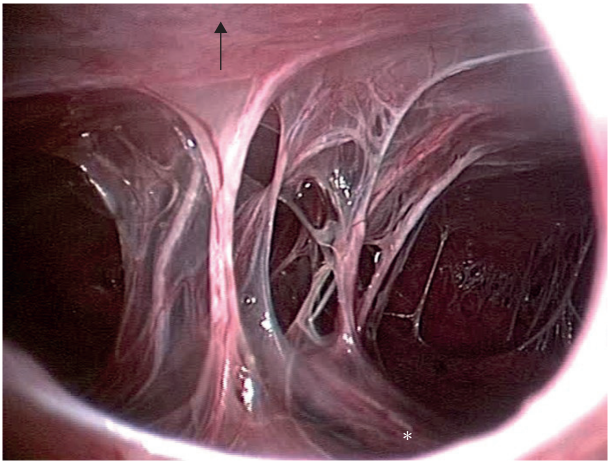


*Figure 3. Pleural adhesions. These can be detected by chest ultrasonography, which is always recommended before MT/P. Arrow: parietal pleura; *: lung.*

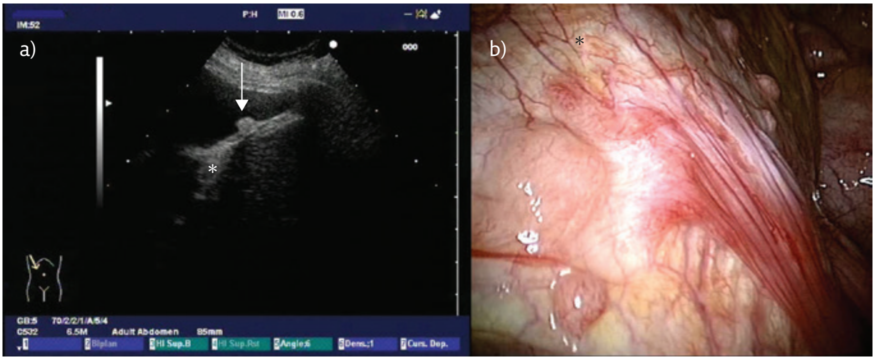


Figure 4. a) Nodule (white arrow) on the surface of the diaphragm (*) can be detected by chest ultrasound. b) Endoscopic view of the same patient with nodules on the surface of the diaphragm (*).

down. Even if the procedure is performed under general anaesthesia, it is mandatory to apply local anaesthesia to the skin, subcutaneous tissues and pleura before the induction of artificial pneumothorax using a pleural needle. A small skin incision followed by blunt dissection is performed to introduce the trocar into the pleural space. A semirigid or rigid thoracoscope can then be inserted and the pleural fluid evacuated, allowing inspection and other interventions in the pleural space (biopsies of the parietal pleura, pulverisation of talc, resection of adhesions, *etc.*) (figure 5). Upon completion of the procedure, a chest tube drain is inserted through the tract

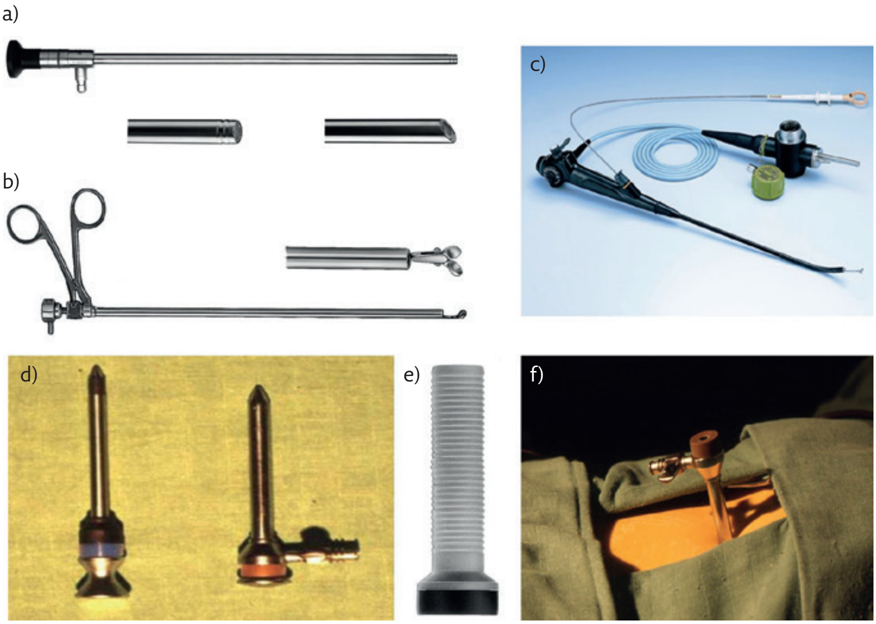


Figure 5. Thoracoscopy instruments. a) Rigid thoracoscope with to different tips (0° and 25° angle). b) Optical biopsy forceps. c) Flexi-rigid thoracoscope. d) Metallic 7- and 5-mm trocars (the latter for coagulating forceps). e) Plastic trocar. f) Trocar after insertion for a MT/P using one single-point entry, which the most common situation. a, b, d and e) Reproduced from Astoul et al. *(2014) with permission from the publisher.*

into the pleural space and connected to a water seal device with gentle suction. In patients who undergo diagnostic thoracoscopy alone, the drain can be removed on the table. If pleurodesis is performed, the drain needs to remain *in situ* for a longer period depending on the aetiology of the pleural effusion.

Clinical indications

Pleural exudates

MT/P is an effective procedure to diagnose the aetiology of a pleural exudate when simple thoracentesis, which is the first step of the management of pleural effusion, does not establish a diagnosis. Indeed, even with the use of HRCT imaging, many patients with exudate do not have focal pleural abnormalities that can be easily identified. The advantages of MT/P compared to closed pleural biopsies or image-guided biopsies is that the physician can visualise the pleura and selectively target areas with abnormal appearance, the majority of pleural abnormalities being preferentially located on the most inferior portions of the posterior parietal pleura or on the diaphragm, particularly for malignant pleural effusion (figure 4b). Consequently, the overall sensitivity of MT/P in this indication is similar to that of VATS performed under general anaesthesia. Another advantage is that the procedure can be combined with a therapeutic procedure to prevent the recurrence of pleural effusion by insufflating dedicated talc, which was found to be the most efficient compound for a pleural symphysis in a recent meta-analysis.

Pneumothorax

Spontaneous pneumothorax is a common clinical problem that, in some cases, can be managed with MT/P. In cases of primary spontaneous pneumothorax (PSP), first-line treatment consists of aspiration or chest tube drainage, but when the pneumothorax is recurrent or in the case of persistent air leak, pleurodesis may be indicated. The best approach remains a matter of debate due to the frequent presence of apical subpleural blebs or bullae, which are thought to contribute to the pathophysiology of the disease despite the lack of evidence for this mechanism. MT/P with talc poudrage in patients with recurrent PSP has been shown to be efficient and safe for the prevention of further episodes.

Parapneumonic effusions and empyema

The initial treatment of empyema consists of antibiotics and chest tube drainage to evacuate the pleural space. However, when chest tube drainage is unsuccessful due to loculations, MT/P should be an alternative to surgery to remove fibrinopurulent membranes, to sever adhesions allowing the creation of a single pleural cavity for efficient drainage and for pleural lavages. However, so far, the role of MT/P in the treatment of pleural space infections remains unclear and each case has to be discussed during a multidisciplinary meeting including thoracic surgeons.

Safety profile of MT/P

The incidence of major complication during medical thoracoscopy is ~1.8% for rigid MT/P and 1.5% with the new flexi-rigid thoracoscope. The major complications can include prolonged air leak, haemorrhage, subcutaneous emphysema, empyema, wound infection, and complications related to the moderate sedation such as arrhythmia or hypotension. The need for open surgery is extremely rare. All these complications can be prevented. While an obliterated pleural space (always detect by chest ultrasonography) is an absolute contraindication, relative contraindications include bleeding disorders, hypercapnia, an unstable cardiovascular status, patients with OSAS and severe COPD patients. By observing the following rules, the majority of these complications can be prevented.

- Postpone MT/P if the patient is coughing
- Measure blood gases and monitor cardiac signs by ECG during the procedure
- Give supplementary oxygen during the procedure
- Avoid taking biopsy from the anterior parietal pleura (internal mammary vessels)
- Coagulate and ensure haemostasis
- Insert a chest tube at the end of the procedure with a gentle suction (<50 cmH_2O) for lung re-expansion

Conclusion

Thoracoscopy is a safe and effective procedure in the assessment and management of pleural diseases. However, it is essential that patients are carefully selected and that their medical status is optimised prior to the intervention. Thoracoscopy is simple to perform but all cases should be performed meticulously in a stepwise approach as outlined here. Physicians must be prepared for all eventualities and, in particular, the chest drain and electrocautery should be available from the outset so that complications can be minimised.

Further reading

- Agarwal R, *et al.* (2013). Diagnostic accuracy and safety of semirigid thoracoscopy in exudative pleural effusions: a meta-analysis. *Chest*; 144: 1857–1867.
- Astoul P, *et al.*, eds. (2014). Thoracoscopy for pulmonologists: a didactic approach. Berlin Heidelberg, Springer-Verlag.
- Bhatnagar R, *et al.* (2016). Advanced medical interventions in pleural disease. *Eur Respir Rev*; 25: 199–213.
- Clive AO, *et al.* (2016). Cochrane corner: interventions for the management of malignant pleural effusions. *Thorax*; 71: 964–966.
- Marchetti G, *et al.* (2015). Ultrasound-guided medical thoracoscopy in the absence of pleural effusion. *Chest*; 147: 1008–1012.
- Medford AR, *et al.* (2010). Thoracic ultrasound prior to medical thoracoscopy improves pleural access and predicts fibrous septation. *Respirology*; 15: 804–808.
- Rodriguez-Panadero F, *et al.* (2006). Thoracoscopy: general overview and place in the diagnosis and management of pleural effusion. *Eur Respir J*; 28: 409–422.
- Rozman A, *et al.* (2014). Semirigid thoracoscopy: an effective method for diagnosing pleural malignancies. *Radiol Oncol*; 48: 67–71.
- Skalski JH, *et al.* (2014). Medical thoracoscopy. *Semin Respir Crit Care Med*; 35: 732–743.

Thoracentesis

Emilio Canalis

Thoracentesis (pleural tap) (figure 1) is a frequently performed procedure that is used to remove pleural fluid. Its goals may be diagnostic and/or therapeutic.

Diagnostic thoracentesis should be performed on almost all patients with a pleural effusion of unknown origin. Its main purpose is to differentiate between transudate and exudate. The number of diagnoses established by pleural fluid analyses varies with the population being evaluated. Careful history and physical examination, radiological evaluation, and ancillary blood tests are crucial in establishing a pre-test diagnosis.

The main purpose of therapeutic thoracentesis is to relieve dyspnoea and respiratory insufficiency caused by pleural effusion.

Patient position

A sitting position is preferred in conscious patients, as this will help the fluid to settle in the posterior and basal regions of the lung (usually the seventh and eight intercostal spaces, although clinical examination may reveal different locations of the fluid).

Once a comfortable position for operating on the patient is achieved, the site for the puncture must be selected. This is decided according to the results of the physical examination and the radiological findings, which will indicate characteristics such as the size and localisation of the main effusion and whether it is free-organised, free-floating or encapsulated. Ultrasound examination is valuable to assess fluid presence accurately.

The puncture should be guided by ultrasound or attempted one intercostal space further down from where dullness on percussion starts. At least in pleural effusions of smaller size, ultrasound guidance is strongly recommended.

The thoracentesis set

The thoracentesis set is detailed in table 1.

Key points

- Thoracentesis may be diagnostic or therapeutic in patients with a pleural effusion.
- Ultrasound examination is valuable in guiding the procedure.
- There are no absolute contraindications, and complications are rare, but the possibility must be taken into account.

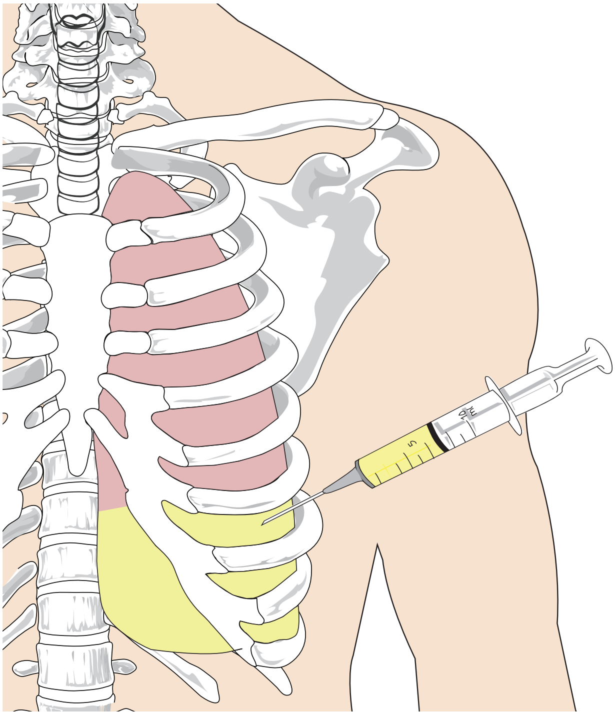


Figure 1. Thoracentesis needle through the intercostal space.

Table 1. Thoracentesis set

Chlorhexidine solution
Sterile drapes, gloves and gauzes
Abbocath-type needle catheters
Local anaesthesia
Syringes
Three-way stopcock
Aspiration set (if therapeutic)
Adhesive strips
Instrumentation table

Procedure

1) Under sterile conditions, the selected region of puncture is disinfected with chlorhexidine or alcohol and a sterile draping, preferably with a center hole, is taped to the patient's back.

2) Local anaesthesia is injected stepwise, at first with an intradermal injection producing a small wheal, then infiltrated subcutaneously and into the intercostal muscle down to the parietal pleura at the upper rim of the lower rib in order to avoid the intercostal nerve and vessels. During the injection, alternating aspiration is performed until the parietal pleura is penetrated and pleural fluid is aspirated. Then, 20–60 mL pleural fluid should be aspirated for fluid analysis.

3) Diagnostic thoracentesis can occasionally be carried out without local anaesthesia if the adult patient is calm, the puncture is anticipated to be easy, the subject is not obese and the operator is experienced.

4) For therapeutic thoracentesis, a catheter should be used, which is immediately connected to a closed three-way stop-cock. This allows aspiration syringes to be changed or facilitates connection to a suction device.

5) As soon as the procedure is finished, the needle or the catheter is removed and pressure is applied to the wound for a few minutes, followed by a sterile dressing.

6) Chest radiography should be carried out to exclude the development of a pneumothorax, unless the procedure has been performed under ultrasound guidance without any problems.

Contraindications

Diagnostic thoracentesis has no absolute contraindications provided that it is performed with caution by experienced persons. The following are relative contraindications:

- Altered coagulation: a decision must be taken as to whether thoracentesis is really needed. If so, it may be necessary to reverse anticoagulation, or to administer fresh frozen plasma or platelets.
- Mechanical ventilation with positive pressure at the end of aspiration. Whenever possible, mechanical ventilation is suspended briefly. If this is not possible, thoracentesis must be carried out with caution using ultrasound guidance.
- Local skin infections such as cellulitis or herpes zoster.
- Small effusions (thoracentesis should be performed under ultrasound control).

Complications

As with any invasive investigation, complications may occur, but these are rare. Patients must be informed about possible complications when asked to give their informed consent. The most important is pneumothorax, which is usually only small if caused by entrance of air into the pleural cavity through the needle or the aspiration system. It can become larger if the lung is injured by the needle.

Further reading

- American College of Surgeons (2004). Chest trauma. *In:* Advanced Trauma Life Support (ATLS) Course Manual. 7th Edn. Chicago, American College of Surgeons; pp. 107–121.
- Dev SP, *et al.* (2007). Videos in clinical medicine. *N Engl J Med*; 73: 948–950.
- Duncan DR, *et al.* (2009). Reducing iatrogenic risk in thoracentesis: establishing best practice via experiential training in a zero-risk environment. *Chest*; 135: 1315–1320.
- Havelock T, *et al.* (2010). Pleural procedures and thoracic ultrasound. British Thoracic Society pleural disease guideline 2010. *Thorax*; 65: Suppl. 2, 261–276.
- Porcel JM, *et al.* (2006). Diagnostic approach to pleural effusions in adults. *Am Fam Physician*; 75: 1211–1220.
- Sachdeva Sheferd LW, *et al.* (2013). Thoracentesis and thoracic ultrasound: state of the art in 2013. *Clin Chest Med*; 34: 1–9.

Chest radiography and fluoroscopy

Walter De Wever

Chest radiography is the most frequently used radiological chest imaging technique and also one of the most challenging. Clinical practice and guidelines for use of chest radiography are influenced by multiple factors such as the clinical context, the confidence of the clinicians, the changing incidence of complications, the availability of alternative imaging techniques, and the experience of the available radiologists and clinicians. Technical aspects of this imaging modality are studied extensively. New approaches to image acquisition and display have been introduced in past decades. As a general rule, establishing the presence of a lung disease process on a radiograph should constitute the first step in radiological diagnosis of chest disease. The lower sensitivity of a chest radiography demands greater accuracy in interpretation. This greater accuracy can be achieved by following a standardised and systemic approach to a complete review of a chest radiograph. Technical factors and the position of the patient should also be considered when a chest radiograph is reported. Comparing prior films with recent ones is mandatory for the evaluation of pulmonary diseases.

Basic radiographic techniques

Diagnostic accuracy in chest disease is partly related to the quality of the radiographic images themselves. Several variables, such as patient position, patient respiration and film exposure factors, must be taken into account to ensure image quality (table 1). A good patient positioning includes:

- X-ray beam properly centred
- patient's body not rotated
- scapulae of the patient rotated so that they are projected away from the lungs

Key points

- Chest radiography is the first step in the radiological diagnosis of chest diseases.
- Chest radiography it is a common technique but achieving high image quality is challenging and depends on getting several factors right (patient and technical parameters).
- The development of digital imaging offers promising opportunities to improve image consistency and data management.

Table 1. Key points to obtain a good chest radiograph

Radiographic appearance

- Frontal view (posteroanterior view)
  - Area from the lower cervical spine to below the costophrenic angles
  - Sternoclavicular joints symmetrical about the midline
  - Shadows of the scapulae away from the lung field
- Lateral view
  - Soft tissues of the axillae should be included

Respiration

- End of normal inspiration

Positioning of the patient

- Erect position
  - Very ill patients: horizontal or semierect
- Posteroanterior position

Film exposure factors

- High kilovoltage
- Focus: film distance
  - Must be kept constant for any particular department
  - 150–180 cm

Patient respiration must be fully suspended, preferably at TLC. Film exposure factors should be such that faint visualisation of the thoracic spine and the intervertebral disks on the posteroanterior radiograph is possible and that lung markings behind the heart are clearly visible. The exposure should be as short as possible, consistent with the production of adequate contrast. A high-kilovoltage technique appropriate to the film speed should be used.

Projections

Posteroanterior and lateral projection

The most satisfactory routine radiographic views for evaluating the chest are the posteroanterior and lateral projections with the patient standing (figure 1). The combination of these two projections provides very good three-dimensional information. In patients who are too ill to stand up, anteroposterior upright or supine projections offer alternative but considerably less satisfactory views. The anteroposterior projection is of inferior quality because of the shorter focal distance, the greater magnification of the heart and often, the restricted ability of these patients to suspend respiration or achieve full inspiration. Based on a review of the literature, and the recommendations of the American College of Radiology and the American Thoracic Society, recommendations on the use of chest radiographs are summarised in table 2.

Lateral decubitus projection

For the lateral decubitus projection, the patient lies on one side and the X-ray beam is oriented horizontally. This technique is particularly helpful for the identification of small pleural effusions. <100 mL of fluid may be identified on well-exposed radiographs in this position. Radiography in the lateral decubitus position is also useful to demonstrate a change in the position of an air–fluid level in a cavity or a freely moving intracavitary loose body (*e.g.* fungus ball in aspergilloma).

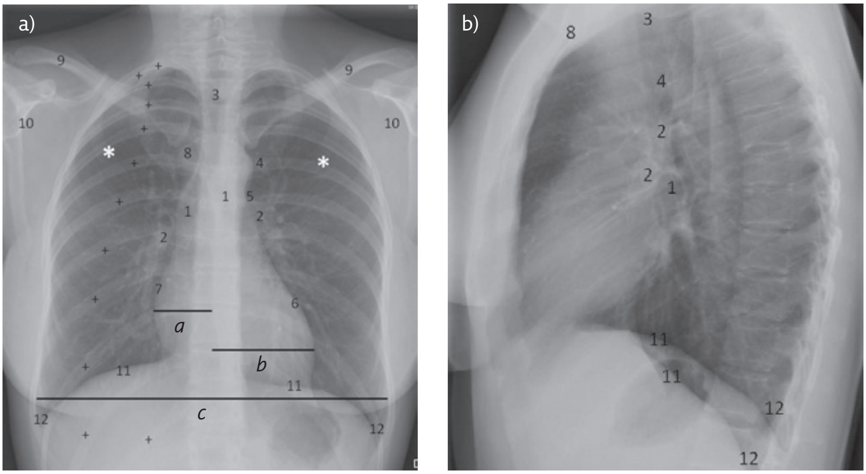


Figure 1. a) Posteroanterior chest radiograph. Normal lungs are visible as black fields (air) (*) with superposition of multiple white linear structures (vessels and walls of airways). The lung hila consist of bronchi (main stem (1) and lobar bronchi) and vascular structures (pulmonary arteries (2) and pulmonary veins). A normal pleura is not visible on a chest radiograph. In the mediastinum, we can visualise the trachea (3) as a translucent tube on the midline, the aortic arch (4), the pulmonary trunk (5), the left border of the heart formed by the left ventricle (6) and the right border of the heart formed by right atrium (7). A normal heart has a normal cardiothoracic index: (a+b)/maximal diameter of the chest (c) must be <0.5. The bony components of the chest visible on the frontal view are: the ribs (+), the manubrium sternum (8), the clavicles (9), the scapulae (10) and the vertebral bodies on the midline. The diaphragm (11) is sharply delineated and the costophrenic angles (12) must be sharp and free. b) Lateral chest radiograph. The lateral chest film can be used to localise better the findings on the frontal view.

Table 2. Recommendations for the use of chest radiography

Indications
Signs and symptoms related to the respiratory and cardiovascular system
Follow-up of previously diagnosed thoracic disease for evaluation of improvement resolution, or progression
Staging of intra- and extrathoracic tumours
Pre-operative assessment of patients scheduled for intrathoracic surgery
Pre-operative evaluation of patients who have cardiac or respiratory symptoms, or patients who have a significant potential for thoracic pathology that may lead to increased peri-operative morbidity or mortality
Monitoring of patients who have life support devices and patients who have undergone cardiac or thoracic surgery or other interventional procedures
No indications
Routine screening of unselected populations
Routine pre-natal chest radiographs for the detection of unsuspected disease
Routine radiographs solely because of hospital admission
Mandated radiographs for employment
Repeated radiograph examinations after admission to a long-term facility

Lordotic projection

The lordotic projection can be made in the anteroposterior or posteranterior projection. For this projection, the patient stands erect and the X-ray tube is angled 15° cephalad. The main advantage of this modification is its reproducibility. The lordotic projection can be used:

- for improving the visibility of the lung apices, superior mediastinum and thoracic inlet
- for identifying the minor fissure in suspected cases of atelectasis of the right middle lobe

Oblique projection

Oblique studies are sometimes useful in locating a pleural or chest wall disease process (*e.g.* pleural plaque); however, in most situations, CT is preferred.

Inspiratory–expiratory radiography

Comparison of radiographs exposed in full inspiration and maximal expiration may supply useful information in two specific situations.

- The first indication is the evaluation of air trapping, either focal or general. With air trapping, diaphragmatic excursion is reduced symmetrically and lung density changes little between expiratory and inspiratory radiographs.
- The second indication is when a pneumothorax is suspected. In the European Respiratory Society task force statement for the diagnosis and treatment of primary spontaneous pneumothorax of 2015, expiratory films are not thought to confer additional benefit in the routine assessment of a pneumothorax. In addition, the German and British guidelines will not recommend expiratory films for the routine detection of pneumothorax. However, when a pneumothorax is suspected and the visceral pleura line is not visible on the standard inspiratory radiograph, or the findings are equivocal, expiratory films can help in the detection of pneumothorax.

Bedside radiography

Chest radiography performed at the bedside with portable apparatus is one of the most frequently performed radiological examinations; however, this technique is also the examination with the most variation in image quality. The amount of diagnostic information provided by chest examinations performed with portable apparatus is high and many abnormalities are detected. These examinations are useful 76–94% of the time. However, poor image quality and day-to-day variations in film density interfere with the detection of interval changes in patients with pulmonary diseases. The interpretation of a bedside radiograph requires extensive radiological experience to avoid misinterpretation of pleural and pulmonary disease. In addition, bedside radiography is an irreplaceable tool for detecting the malposition of tubes and lines, and to identify associated complications. The need to improve the image quality of this examination has long been recognised but it is a difficult problem to solve.

Digital chest radiography

There have been many remarkable advances in conventional thoracic imaging over the past decade. Perhaps the most remarkable is the rapid conversion from film-based to digital radiographic systems. Digital radiography is the common name for different technologies that are characterised by a direct readout matrix that covers the whole exposure area. Conversion of X-ray intensity into electrical signals can either be direct (selenium-based systems) or indirect (scintillator/photodiode systems). Advantages of digital radiography systems are:

- high image quality
- the potential for dose reduction

This technique is now the preferred imaging modality for bedside chest imaging because of its more consistent image quality. Digital radiography is rapidly replacing film-based chest units for in-department posteroanterior and lateral examinations. The final aim is to realise a completely integrated digital radiology department throughout the hospital connected to a large digital image archiving system. This concept, referred to as picture archiving and communication systems, represents the logical culmination of the extensive research that is continuing in this area.

New developments in chest radiography

With the introduction of digital radiography, development of new techniques became possible. These techniques are dual energy, temporal subtraction, rib suppression technique and digital tomosynthesis.

Dual energy

Dual energy involves weighted subtraction of low- and high-energy images, and results in images representing bone structures or soft tissue. This technique can improve the detection of small, noncalcified pulmonary nodules and the detection of calcified chest lesions. Disadvantages of this technique are the higher radiation dose compared with standard digital radiography, the reduced signal to noise ratio and the need for additional hardware to perform this technique.

Temporal subtraction

Temporal subtraction involves subtraction of a current image from a prior image of the same patient. With this technique, the detection of pathological changes over time becomes easier. Sophisticated algorithms are needed to eliminate detection errors caused by differences in matching the projections of the two examinations.

Rib suppression technique

Rib suppression is a processing technique that suppresses ribs in the image. Advantages of this technique over dual energy are:

- no need for an additional radiation dose or specialised equipment
- noise levels are not increased

Eliminating ribs has already shown to be effective in detection of lung lesions.

Digital tomosynthesis

Digital tomosynthesis is a tomographic technique producing cross-sectional images using a digital detector and a chest radiography system with a moving X-ray tube. This technique can improve the detection of pulmonary nodules with higher sensitivity than chest radiography by producing cross-sectional images without overprojection of ribs or overlying vascular structures and can be an alternative to CT as a low-dose, low-cost technique.

Chest fluoroscopy

Chest fluoroscopy was a popular procedure a generation ago. Patients were examined fluoroscopically in various projections and multiple spot radiographs were obtained with barium in the oesophagus. Examinations to evaluate pericardial effusion also were frequent. Overall diminution in cardiac pulsation and greater pulsation of the posterior cardiac wall in the lateral projection were thought to be signs of effusion. Other indications for fluoroscopy included the investigation of foreign bodies determined by air trapping and appropriate mediastinal shift, and the evaluation of diaphragmatic paralysis. This evaluation of diaphragmatic paralysis is still an indication for fluoroscopy today.

Dose and image quality in chest radiography

The radiation dose to the patient for chest radiography is relatively low but because of its frequent use, the collective dose can be considerable. The effective dose of a posteranterior chest radiograph is ~0.02 mSv, which is about 0.5% that of a CT scan of the chest. The effective dose related to the lateral chest image is approximately two times higher compared with the dose of a posteranterior projection. Studies indicate that dose reduction in posteroanterior chest images to at least 50% of commonly applied dose levels does not affect diagnosis in lung fields; however, dose reduction in the mediastinum, upper abdomen and retrocardiac areas appears to directly deteriorate diagnosis.

Further reading

- American College of Radiology (1997). ACR Standard for the Performance of Pediatric and Adult Chest Radiography. Reston, ACR.
- American Thoracic Society (1984). Chest X-ray screening statements. *Am Thorac News*; 10: 14.
- Eisenhuber E, *et al.* (2012). Bedside chest radiography. *Respir Care*; 57: 427–443.
- MacMahon H, *et al.* (1991). Digital chest radiography. *Clin Chest Med*; 12: 19–32.
- Raoof S, *et al.* (2012). Interpretation of plain chest roentgenogram. *Chest*; 141: 545–558.
- Rigler LG (1931). Roentgen diagnosis of small pleural effusions: a new roentgenographic position. *JAMA*; 96: 104–108.
- Schaefer-Prokop C, *et al.* (2003). Digital radiography of the chest: detector techniques and performance parameters. *J Thorac Imaging*; 18: 124–137.
- Veldkamp WJ, *et al.* (2009). Dose and perceived image quality in chest radiography. *Eur J Radiol*; 72: 209–217.
- Wandtke JC (1994). Bedside chest radiography. *Radiology*; 190: 1–10.
- Zinn B, *et al.* (1956). The lordotic position in fluoroscopy and roentgenography of the chest. *Am J Roentgenol Radium Ther Nucl Med*; 75: 682–700.
- Andronikou S, *et al.* (2017). Guidelines for the use of chest radiographs in community-acquired pneumonia in children and adolescents. *Pediatr Radiol*; 47: 1405–1411.
- Ferrari A, *et al.* (2018). Digital chest tomosynthesis: the 2017 updated review of an emerging application. *Ann Transl Med*; 6: 91.
- Tschopp JM, *et al.* (2015). ERS task force statement: diagnosis and treatment of primary spontaneous pneumothorax. *Eur Respir J*; 46: 321–335.
- MacDuff A, *et al.* (2010). Management of spontaneous pneumothorax: British Thoracic Society pleural disease guideline 2010. *Thorax*; 65: Suppl. 2, ii18–ii31.
- Schnell J, *et al.* (2018). Management of spontaneous pneumothorax and postinterventional pneumothorax: German S3-guideline. *Zentralbl Chir*; 143: Suppl. 01, S12–S43.

Transthoracic ultrasound

Jane A. Shaw, Florian von Groote-Bidlingmaier and
Coenraad F.N. Koegelenberg

Transthoracic ultrasound (TUS) has emerged as an essential tool for the respiratory physician. It is invaluable in the assessment of lesions of the chest wall, pleural disease, intrapulmonary or mediastinal lesions which adjoin the pleura, diaphragmatic abnormalities, lung consolidation and interstitial syndromes. The use of TUS guidance has markedly improved the safety and efficacy of transthoracic procedures, and point-of-care TUS in the emergency and critical care settings is viewed as a core clinical skill. The utility of TUS relies on the technical competency of the clinician. In the right hands TUS is rapid, portable, cost-effective and accurate, with the added benefit of being radiation-free.

Basic principles

Ultrasound waves are high frequency sound waves which are readily propagated in liquids and tissues with high density, but are poorly propagated in air. Ultrasound waves reflect off interfaces between structures with dissimilar densities, generating 'echoes'. An ultrasound machine transmits an electrical impulse into crystals

Key points

- Transthoracic ultrasound can be performed with the most basic ultrasound equipment and allows for rapid, mobile, cost-effective and radiation-free assessment of patients with a wide variety of respiratory diseases.
- Point-of-care ultrasound can provide valuable information in the emergency and critical care setting.
- The major indications for the use of transthoracic ultrasound in the acute setting include the diagnosis of a pneumothorax, assessment of lung consolidations, interstitial syndromes and pulmonary embolism.
- Other important applications of transthoracic ultrasound include the description of pleural effusions, pleural thickening, chest wall lesions, intrapulmonary and pleural tumours, and the identification of diaphragmatic dysfunction.
- Ultrasound is essential to guide thoracentesis, drainage of effusions and other thoracic interventions.
- Transthoracic ultrasound is an operator-dependant imaging modality which requires understanding of both the basic principles of image generation and training in recognition of normal and abnormal appearances of the thoracic structures.

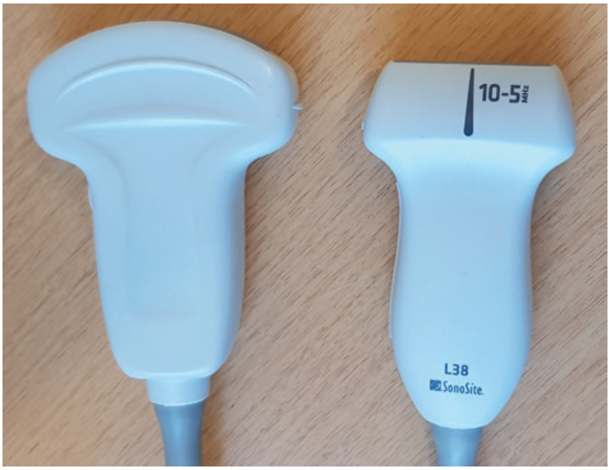


Figure 1. Two types of probes commonly used for transthoracic ultrasound. The low frequency curvilinear probe (left) which is used for basic screening, assessment of pleural effusions and lesions deeper within the chest, and the high frequency linear probe (right) which is used for detailed delineation of the lung–pleura interface.

embedded within the transducer, which generate an ultrasound wave of a specific frequency as the impulse causes them to deform. Similarly, mechanical deformation of the crystals by the returning echo generates information such as amplitude and time taken to return, which is interpreted by the processing unit as brightness, depth, *etc.*, and used to construct a visual representation on the screen. The echogenicity of a structure is determined by the amplitude of its echo. Ultrasound probes vary in the frequency of ultrasound wave emitted and the plane in which the crystals are aligned. Lower frequencies have good depth penetration but lower resolution, while higher frequencies produce better resolution but cannot penetrate to a great depth. A probe with a flat crystal alignment will produce a rectangular image with uniform resolution; a probe with a curvilinear alignment will generate a wedge-shaped image with lower lateral resolution. Commonly used probes (figure 1) include: the 2–5 MHz curvilinear probe (for basic screening and visualising structures deeper in the chest); the 6–12 MHz linear probe (for high resolution images of the lung–pleura interface); and the 1–5 MHz phased array probe (useful in patients with a large body habitus). A standard ultrasound machine has at least two modalities, which differ in the manner of ultrasound wave emission and translation and, therefore, produce vastly different images. Conventional scanning is performed in B-mode (brightness mode), which generates a simple two-dimensional slice of the structures being imaged. M-mode (motion mode) will generate a representation of the motion of a structure in the plane of the probe over time, and is particularly useful in excluding pneumothorax. Some ultrasound machines include Doppler modes, which allow the differentiation of the direction of motion of sound waves and can be useful in assessing vascular structures.

Technical aspects

Positioning

The importance of positioning and environment in performing a TUS cannot be overemphasised. The environment should be one in which the patient's chest can be exposed, and the ambient light can be manipulated. The screen and the patient should be in the same visual plane of the physician. The patient should be comfortable in the optimal position for examination of the area of interest: the posterior chest is ideally scanned in the sitting position whereas the anterior and lateral chest are best examined in the supine or lateral decubitus positions. The TUS probe is held between three fingers of one hand, the hand resting comfortably on the patient's chest, stabilised by the other fingers. Probe orientation (longitudinal or transverse scanning) is at the physician's discretion, provided the indicator marker on the lateral aspect of the probe corresponds to the side of the marker on the screen.

Image optimisation

The TUS image should be optimised for the structure being evaluated by appropriate probe selection and by adjusting settings such as depth and gain. Adjusting the depth simply allows the physician to choose the focal point of the examination. The resolution of shallow structures improves when the depth is limited. The ultrasound screen will have a centimetre scale along one side, as well as a cursor measurement function. Accurate depth measurement can be critical in ensuring the safety of procedures where deep structures are at risk of laceration by a biopsy needle or trocar. The gain parameter refers to the brightness of the image on the screen (but has no effect on resolution). Some ultrasound machines allow the gain to be increased at a focal point deeper within the image, counteracting the usual decrement in brightness that occurs with increasing depth.

Normal TUS

For competency in TUS, familiarity with the normal appearance of the thoracic structures is mandatory (figure 2). The soft tissues of the chest wall are seen as a series of hyperechoic lines at the top of the ultrasound image. In the longitudinal probe orientation, the ribs will be visible as short curved hyperechoic lines with acoustic shadows (hypoechoic spaces) underneath. This appearance of the ribs is absent in transverse probe orientation. The pleura is identified as a single hyperechoic line, which will be between and just below the ribs when the probe is held longitudinally. The two layers of the pleura are usually perceived as a single line. Normal pleura seen at high resolution will demonstrate the dynamic 'lung sliding' sign: the movement of the visceral pleural surface against the parietal pleural surface during the respiratory cycle. Alternate descriptions include 'ants crawling' or a shimmering or sparkling along the pleural line. Lung sliding can also be appreciated in M-mode as the 'sea shore' pattern, with horizontal lines above the pleural line (the sea) and a granular appearance below it (the sand). Ultrasound cannot visualise normal aerated lung tissue, so it appears uniformly hypoechoic. However, artefacts from the lung–pleura interface may be visible within the hypoechoic area in the normal TUS. The large change in acoustic impedance at the lung–pleura interface causes horizontal reverberation artefacts that are seen as a series of echogenic parallel lines equidistant from one another below the pleura, known as A-lines (figure 2). Another important artefact from the lung–pleura interface, but which usually indicates abnormal underlying lung, is the presence of B-lines. These are vertical reverberation artefacts, seen as discrete laser-like hyperechoic lines originating from the pleural line and extending with uniform intensity to the bottom of the screen (figure 3). B-lines move synchronously with lung sliding, and are thought to represent areas of partially deaerated lung or fluid-filled interlobular septae. Other vertical reverberation artefacts called Z-lines or 'comet tails' may also be present. Z-lines fade before the edge of the screen, do not move with respiration, and are not always pathological. The competent TUS user will also familiarise themselves with other artefacts commonly noted in TUS, such as posterior acoustic enhancement, refraction artefact and mirror imaging.

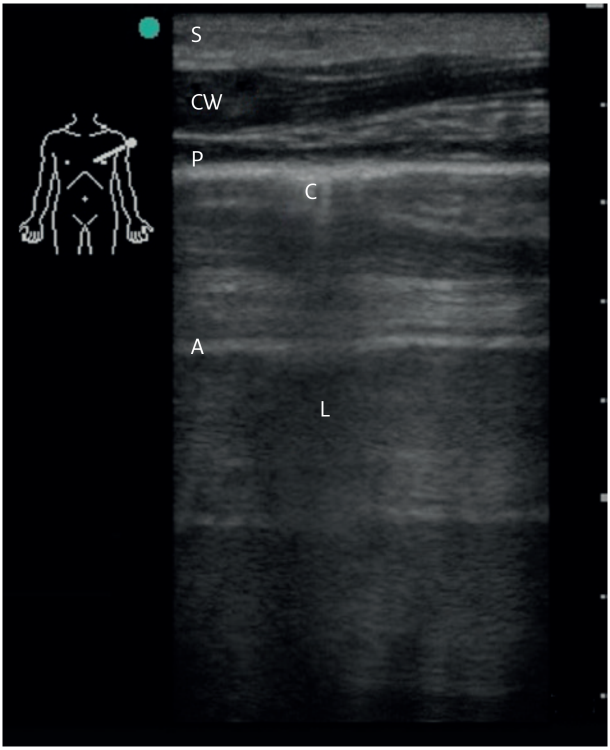


Figure 2. *High frequency ultrasound image obtained from a normal chest. Note the skin (S), chest wall (CW), pleura (P) and lung (L). A-lines (A) and small comet-tail artefacts (C) are present.*

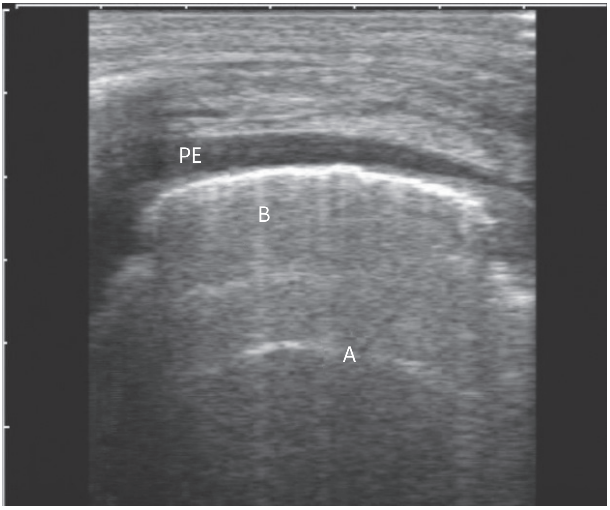


Figure 3. *High frequency ultrasound obtained from a patient with acute left ventricular failure. Note the prominent B-lines (B, vertical to the pleura) crossing the A-lines (A). Also note the small pleural effusion (PE).*

Abnormal TUS

Chest wall disease

Soft-tissue lesions (figure 4), such as lymph nodes, abscesses, haematomas and metastases, can be detected by TUS, often with greater precision than other imaging modalities. Distinguishing between reactive and malignant lymphadenopathy may be possible, with the former appearing as oval or triangular densities, surrounded by a capsule and with a regular central hilum, while the latter tend to be oval in shape with irregular borders, disrupted capsules and distorted vascularisation. The primary benefit of visualising lymph nodes with the TUS is that it allows for safe and accurate fine-needle aspiration or biopsy. Bony lesions are also appreciable with the TUS. Metastases are hypoechoic masses which disrupt the normal structure of a rib, and rib fractures appear as a discontinuity in the outer cortex. TUS can assist in staging of lung cancers by assessing infiltration of the chest wall with a high degree of accuracy.

Pleural effusion

TUS is more sensitive than decubitus radiographs at demonstrating minimal or loculated pleural effusions. The ultrasound appearance of a pleural effusion (figure 5) is highly variable, with few findings that are specific for a particular aetiology. Four appearances based on the internal echogenicity are recognised: 1) anechoic, 2) complex non-septated, 3) complex and septated, and 4) homogenously echogenic (figure 6). Malignant effusions are frequently anechoic. Inflammatory effusions are often associated with strands of echogenic material and septations.

The volume of a pleural effusion can be classified as follows: 1) minimal, if the echo-free space is confined to the costophrenic angle; 2) small, if the space is greater than the costophrenic angle but still within the range of the area covered with a 3.5-MHz curvilinear probe; 3) moderate, if the space is greater than a one-probe range but within a two-probe range; and 4) large, if the space is bigger than a two-probe range.

Pleural disease

Metastatic pleural tumours and malignant mesothelioma can be visualised as polypoid pleural nodules or irregular sheet-like pleural thickening, which may be associated

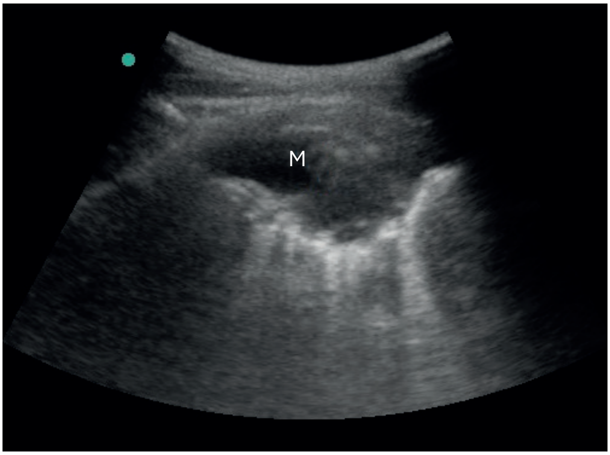


Figure 4. Low frequency ultrasound image of a chest wall mass (M).

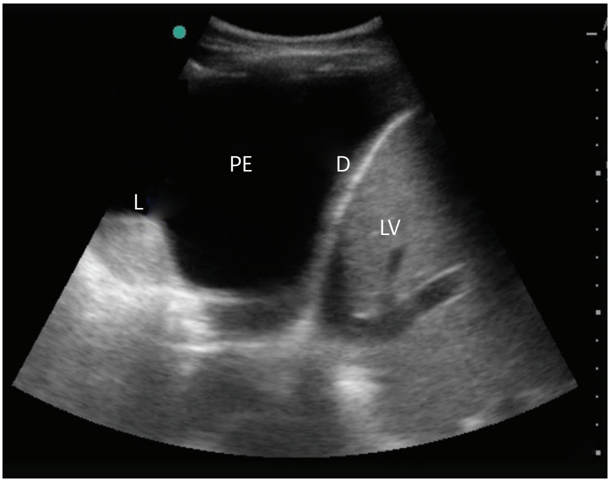


Figure 5. Low frequency ultrasound image of a classical anechoic pleural effusion. Note the pleural effusion (PE), atelectatic lung (L), liver (LV) and diaphragm (D).

with pleural effusions (figure 7). Benign pleural tumours tend to be well-demarcated, noninvasive hypoechoic structures. Pleural plaques may be seen as distinct areas of thickening, possibly calcified. Significant pleural thickening >1 cm, nodularity and diaphragmatic thickening are features which have been strongly associated with pleural malignancy.

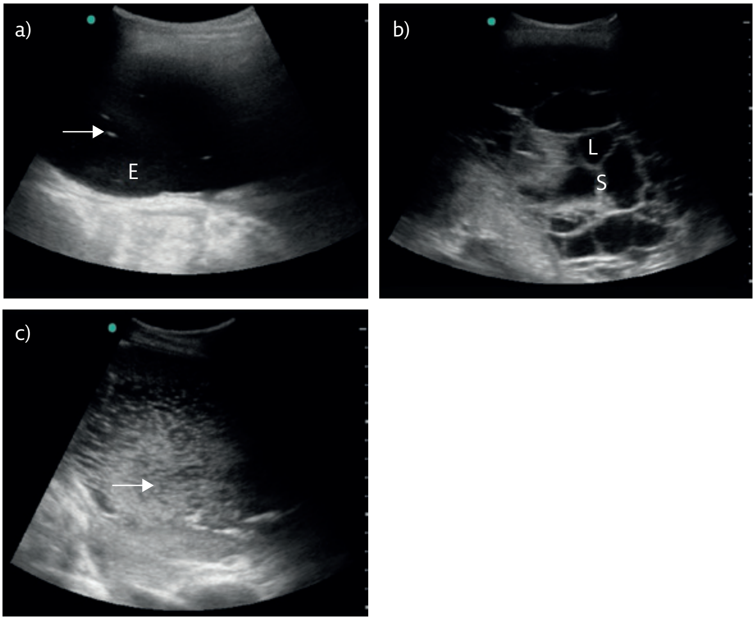


Figure 6. a) A complex non-septated effusion (E) showing some internal echoic "white" debris that may or may not be swirling (arrow). b) A complex septated effusion with numerous septae (S) and locations (L). c) An extreme example of a diffuse homogenously echogenic effusion (arrow) in a patient with long-standing empyema.

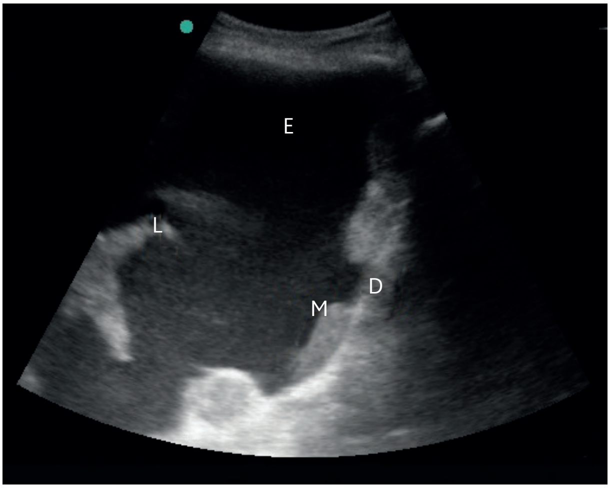


Figure 7. Low frequency scan from a patient with a malignant pleural effusion. Note the large effusion (E) with atelectatic lung (L), and the malignant deposits (M) on the diaphragm (D).

Pneumothorax

TUS may be more sensitive than chest radiography for the diagnosis of pneumothorax and is of particular importance in the various point-of-care ultrasound protocols. Signs which may indicate the presence of a pneumothorax include:

- the presence of a lung point (the dynamic zone of transition between abnormal and normal lung–pleura interface);
- the presence of an air–fluid interface (in a hydropneumothorax or haemopneumothorax);
- the absence of normal lung sliding;
- the absence of a lung pulse (transmitted impulses from heartbeats);
- the absence of B-lines;
- exaggerated A-lines.

Importantly, the presence of lung sliding, the presence of B-lines and the presence of a lung pulse are all signs which can exclude pneumothorax in the lung zone being examined.

Lung ultrasound

Extravascular lung water may be identified by the presence of multiple (more than three per rib space in longitudinal probe orientation), diffuse (in at least two regions of the lung) bilateral B-lines. The distribution of the B-lines and the presence or absence of alveolar consolidations allow for the differentiation of non-cardiogenic from cardiogenic pulmonary oedema (figure 3). Interstitial lung diseases generate multiple B-lines and a fragmented pleural line.

A lung tumour (figure 8) abutting the pleura will be detectable as a hypoechoic mass with posterior acoustic enhancement. Pulmonary consolidations (figure 9) may be detected in early stages as diffusely echogenic tissue which is similar in texture to the liver. Both air and fluid bronchograms are usually seen within the consolidated lung.

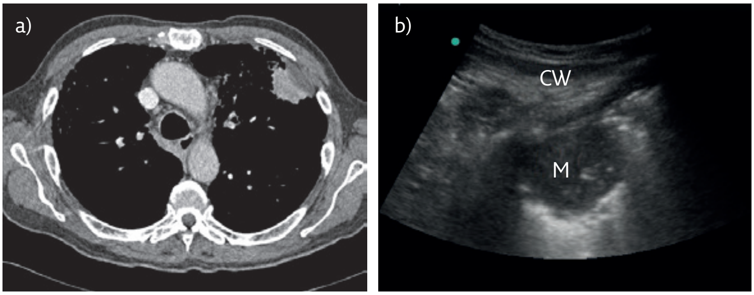


Figure 8. a) CT scan showing a peripheral lung mass and b) the corresponding ultrasound image of the chest wall (CW) and pulmonary mass (M).

Non-infective causes of consolidations with similar appearance on ultrasound include pulmonary infarction, haemorrhage and adenocarcinoma *in situ*.

A hypoechoic lesion with a well-defined or irregular wall adjoining the pleura might represent a lung abscess. The centre of the abscess is most often anechoic but may reveal septations and internal echoes. Cysts commonly appear as large, round anechoic lesions and may demonstrate aetiology-specific features such as 'hydatid sand'.

Conclusion

The value of ultrasound for chest physicians is firmly established. Basic thoracic ultrasonography is an elegant and inexpensive investigation that extends the physicians' diagnostic and interventional potential at the bedside in peripheral lung, pleural and chest wall disease. Respiratory physicians should be confident in the routine use of this imaging modality.

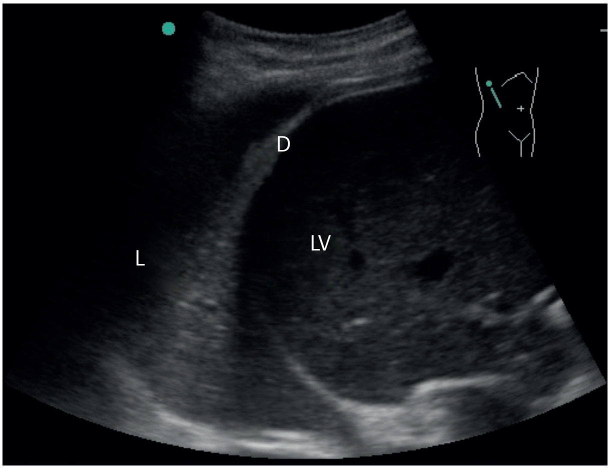


Figure 9. A low frequency ultrasound obtained from a patient with pneumonia. Note the consolidated lung (L) with an echogenicity very similar to the liver (LV) seen below the diaphragm (D).

Further reading

- Corcoran JP, *et al.* (2017). State of the art thoracic ultrasound: intervention and therapeutics. *Thorax*; 72: 840–849.
- Diacon AH, *et al.* (2005). Transthoracic ultrasound for the pulmonologist. *Curr Opin Pulm Med*; 11: 307–312.
- Ding W, *et al.* (2011). Diagnosis of pneumothorax by radiography and ultrasonography: a meta-analysis. *Chest*; 140: 859–866.
- Havelock T, *et al.* (2010). Pleural procedures and thoracic ultrasound: British Thoracic Society pleural disease guideline 2010. *Thorax*; 65: Suppl. 2, 61–76.
- Koegelenberg CF, *et al.* (2008). Pleural ultrasound. *In:* Light RW, *et al*. eds. Textbook of pleural disease. 2nd Edn. London, Hodder & Stoughton, pp. 271–228.
- Koegelenberg CF, *et al.* (2011). Pleural controversy: closed needle pleural biopsy or thoracoscopy – which first? *Respirology*; 16: 738–746.
- Laursen CB, *et al.*, eds (2018). Thoracic Ultrasound. ERS monograph. Sheffield, European Respiratory Society.
- Lichtenstein DA, *et al.* (1995). A bedside ultrasound sign ruling out pneumothorax in the critically ill. *Chest*; 108: 1345–1348.
- Mathis G (1997). Thoraxsonography – part I: chest wall and pleura. *Ultrasound Med Biol*; 23: 1131–1139.
- European Federation of Societies for Ultrasound in Medicine and Biology (2008). Minimal training requirements for the practice of medical ultrasound in Europe. Appendix 11: Thoracic Ultrasound. www.efsumb.org/blog/archives/1687
- Quershi NR, *et al.* (2009). Thoracic ultrasound in the diagnosis of malignant pleural effusion. *Thorax*; 64: 139–143.
- Reissig A, *et al.* (2001). Sonography of lung and pleura in pulmonary embolism: sonomorphologic characterization and comparison with spiral CT scanning. *Chest*; 120: 1977–1983.
- Reissig A, *et al.* (2014). Lung ultrasound in community-acquired pneumonia and in interstitial lung diseases. *Respiration*; 87: 179–189.
- Salamonsen M, *et al.* (2013). Physician performed ultrasound can accurately screen for a vulnerable intercostal artery prior to chest drainage procedures. *Respirology*; 18: 942–947.
- Salamonsen MR, *et al.* (2014). Novel use of pleural ultrasound can identify malignant entrapped lung prior to effusion drainage. *Chest*; 146: 1286–1293.
- Soldati G, *et al.* (2019). The role of ultrasound lung artifacts in the diagnosis of respiratory diseases. *Expert Rev Respir Med*; 13: 163–172.
- Volpicelli G (2011). Sonographic diagnosis of pneumothorax. *Intensive Care Med*; 37: 224–232.
- Volpicelli G, *et al.* (2012). International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med*; 38: 577–591.
- Wallbridge P, *et al.* (2018). Diagnostic ultrasound for acute respiratory failure. *Respir Med*; 141: 26–36.
- Yeh H, *et al.* (1990). Anatomic variations and abnormalities in the diaphragm seen with US. *Radiographics*; 10: 1019–1030.

Lung CT and MRI

Johny A. Verschakelen

CT is the second most important imaging modality of the chest and is, together with chest radiography, one of the two basic imaging techniques used to visualise the lungs. Although there are indications to perform a CT of the chest in patients with a normal chest radiograph, this examination usually succeeds a chest radiograph on which a lesion is seen or suspected.

Except for visualisation of the heart and great vessels, MRI of the chest is less frequently used in daily clinical practice but, in selected cases, this imaging technique can sometimes add information to what is seen on CT.

Computed tomography

Since its introduction, CT has undergone several technical changes and improvements. The first scanners were 'incremental' CT scanners: in order to complete one cross-sectional image, the patient needed to suspend respiration for a few seconds. After that, the table was moved and the next scan was performed. Spiral scanning (also known as helical or continuous volume scanning) has radically altered CT scanning protocols. In this technique, there is continuous patient movement with simultaneous scanning by a constantly rotating X-ray tube and detector system. While the first spiral CT scanners had only one row of detectors, today's scanners have multiple rows (multislice, multirow or multidetector row CT). This allows for a fast simultaneous acquisition of multiple images in the scan plane with one rotation of the X-ray tube around the patient. In this way, very good blood vessel opacification becomes possible using a limited amount of contrast (figure 1). Spiral CT also offers flexible image reconstruction options, such as reconstructing images at various image thicknesses and two- and three-dimensional reconstructions. The advantages of spiral CT are listed in table 1.

Key points

- CT is the second most important imaging modality of the chest.
- CT diagnosis of lung diseases is based on the study of their appearance and distribution patterns together with a careful analysis of patient data.
- CT interpretation of diffuse and interstitial lung diseases requires a formal multidisciplinary approach.
- MRI is second to CT when it comes to visualising pulmonary structure and pathology.

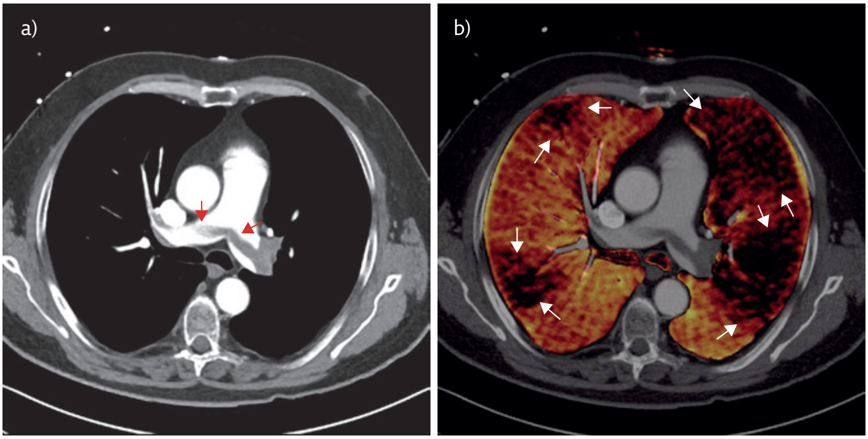


Figure 1. Dual-energy multislice spiral CT acquisition technique in a patient with pulmonary embolism. a) An enhancement defect is seen reaching from the left to the right main stem of the pulmonary arteries (arrows), extending downwards and to the origin of both upper lobe arteries. b) The perfusion scan shows several triangular areas of decreased lung perfusion (arrows).

Table 1. Advantages of spiral CT

Sectional imaging without superposition of structures
Rapid acquisition within one breath hold
Very good blood vessel opacification in vascular studies using a limited amount of contrast
No respiratory misregistration between scans, improving nodule detection
Fast and high-quality multiplanar and three-dimensional reconstructions

Thin-section CT or HRCT is a special type of acquisition technique that uses 0.5–1-mm slice thickness and high-frequency reconstruction algorithms to produce highly detailed images. It is used when detailed information on the lung parenchyma is needed. Spiral CT makes it possible to produce a continuous set of thin slices of the entire chest. In a few seconds, a continuous dataset of the chest is obtained that allows not only the production of axial slices but also the calculation of additional slices in different imaging planes. An important drawback may be the radiation dose. However, the lung parenchyma is very suitable for reduction of the radiation dose without important quality loss, while modern CT scanners have also allowed a substantial reduction in dose. In addition, new reconstruction algorithms such as iterative reconstruction have been developed, which allow further dose reduction without important loss in image quality.

Low-dose CT has been used in several lung cancer screening trials to examine whether any survival benefit can be found in patients with screen-detected cancers compared with the unscreened. At this moment, lung cancer screening has already started in the USA and it is expected that implementation will start in some countries in Europe soon too, once organisational issues have been solved.

As already mentioned, a CT of the chest is usually performed when the chest radiograph is abnormal or suspicious for the presence of pathology, although there are indications for doing this examination even when the chest radiograph does not show any (obvious) abnormalities. Table 2 lists the most frequent indications for a CT of the chest.

Generally, the diagnosis of lung disease on a chest CT is based on three elements: 1) recognition of the appearance pattern of the disease, *i.e.* classifying the abnormalities into a category that is based on their appearance; 2) determination of location and distribution of the abnormalities in the lung, *i.e.* the distribution pattern; and 3) careful analysis of the patient data that are available at the time the CT scan is performed. Although in some cases a diagnosis or a narrow differential diagnosis list can be proposed purely based on the study of the appearance and the distribution pattern of the disease on CT, the abnormalities seen in the lung should be carefully correlated with observations made on other radiological examinations and with all clinical data that are available at the time of the CT examination. Particularly, diffuse and interstitial lung diseases are often very difficult to diagnose when the interpretation is only based on the CT presentation. Ideally, cooperation should be established between the clinician who is responsible for the patient, the radiologist and, when pathological information is present or probably required, the pathologist.

Continuous efforts are made to improve image quality and the diagnostic performance of CT imaging of the lung. Dual-energy CT scanning is helpful to study pulmonary perfusion in patients with subsegmental pulmonary embolism (figure 1). A further increase in the number of detector rows is feasible, which may reduce acquisition time and improve image quality. Automated and semi-automated software packages will help to interpret the CT images.

Magnetic resonance imaging

Like CT, MRI produces multiplanar cross-sectional images, but allows for a greater tissue characterisation because it has a better contrast resolution than CT (figure 2). It also has the benefit of not using ionising radiation. However, except for some special acquisition techniques, spatial resolution of MRI is lower than the spatial resolution of CT.

In MRI, tissue protons are exposed to a strong external magnetic field and realign along the plane of the magnetic gradient. From this position they are then deflected

Table 2. Indications for CT of the chest

Abnormal chest radiograph
Further evaluations of a chest wall, pleural, mediastinal or lung abnormality seen on a chest radiograph
Rule out or confirm a lesion seen on a chest radiograph
Lung cancer staging and follow-up
Assessment of thoracic vascular lesions
Normal chest radiograph
Detection of diffuse lung disease
Detection of pulmonary metastases from a known extrathoracic tumour
Demonstration of pulmonary embolism
Investigation of a patient with haemoptysis
Investigation of patients with clinical evidence of a disease that might be related to the presence of chest abnormalities (*e.g.* pulmonary infection in an immunocompromised patient with fever)

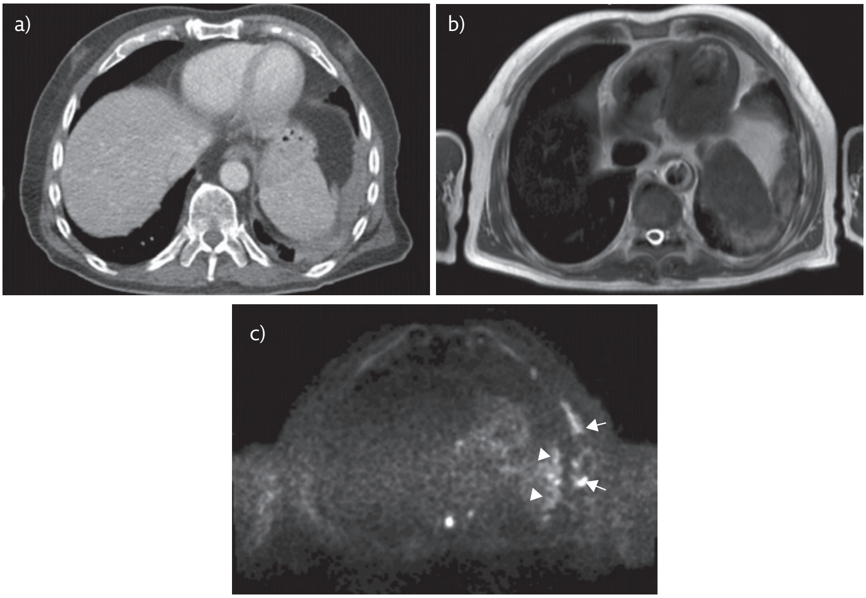


Figure 2. Patient with a left-sided malignant mesothelioma. Both a) CT and b) MRI show the irregular and nodular pleural thickening. There is suspicion of invasion in the diaphragm and spleen. c) Diffusion-weighted MRI shows increased signal in the spleen (arrowheads) indicating tumour invasion in this structure. In addition, increased signal is shown in the chest wall (arrows), suggesting chest wall invasion.

momentarily by applying a so-called radiofrequency (RF) pulse. As they return to their original alignment, the protons emit a faint electromagnetic signal, which is detected by a receiving RF coil. When, in addition, a suitable gradient along the magnetic field is installed, signal detection can be confined to a pre-selected body plane. Processing of these data then yields a sectional image of the plane of interest.

Today MRI has an established role in the imaging of the heart and the great thoracic vessels. For the chest wall, diaphragm, mediastinum and lung, MRI was, for many years, considered a useful 'problem-solving' technique in specific instances, in addition to CT. These instances included the identification of tumour invasion in the chest wall and mediastinal structures, the differentiation between solid and vascular hilar masses, the assessment of diaphragmatic abnormalities, and the study and follow-up of mediastinal lymphoma during treatment. As already mentioned, nowadays multidetector spiral CT is generally used for thoracic imaging, including the areas thought previously to be the domain of problem-solving MRI. However, in patients who are allergic to intravascular iodine CT contrast material or who have renal insufficiency, and who would need a contrast-enhanced CT of the chest, or in cases where radiation should be avoided, MRI of the chest may be considered as an alternative examination.

Although it has become clear now that MRI will always be second to CT when it comes to the visualisation of pulmonary structure, disease and patterns with high spatial resolution, the many research and development efforts that have been made during recent years have resulted in new and valuable applications that are very promising and that could be implemented in clinical practice. There has been much interest in the role of MRI in the diagnosis of pulmonary embolism as a radiation-free alternative to CT.

Some studies have shown that direct visualisation of the thrombus in the pulmonary artery is possible, while others have concentrated on the study of lung perfusion, looking for decreased signal areas in the lung representing underperfused lung tissue on gadolinium-enhanced MRI. In addition, imaging of pulmonary ventilation by MRI has become possible. Hyperpolarised helium-3 gas, hyperpolarised xenon-129 and fluorine- and oxygen-enhanced lung MRI have been used successfully to demonstrate ventilation changes in patients with asthma, COPD and CF, and have opened the field of imaging pulmonary ventilation by MRI. Diffusion-weighted magnetic resonance is another interesting application. This technique provides a measurement that reflects the random Brownian motion of water protons in biological tissue. This motion causes magnetic resonant signal loss that can be measured with the use of diffusion-sensitive sequences and that can be quantified by calculating the apparent diffusion coefficient. In the chest, it has been used successfully to differentiate between malignant and benign lesions.

Currently, most of these techniques remain in the experimental domain or are used in a limited number of centres, but it can be expected that some of them will reach daily clinical practice soon.

Further reading

- Bach PB, *et al.* (2007). Computed tomography screening and lung cancer outcomes. *JAMA*; 297: 953–961.
- Benamore RE, *et al.* (2008). Imaging of pleural disease. *Imaging*; 20: 236–251.
- Brown LR, *et al.* (1991). Masses of the anterior mediastinum: CT and MR imaging. *AJR Am J Roentgenol*; 157: 1171–1180.
- Chiles C, *et al.* (2005). Vascular diseases of the thorax: evaluation with multidetector CT. *Radiol Clin North Am*; 43: 543–569.
- Coolen J, *et al.* (2012). Malignant pleural disease: diagnosis by using diffusion-weighted and dynamic contrast-enhanced MR imaging – initial experience. *Radiology*; 263: 884–892.
- de Hoop B, *et al.* (2009). A comparison of six software packages for evaluation of solid lung nodules using semi-automated volumetry: what is the minimum increase in size to detect growth in repeated CT examinations. *Eur Radiol*; 19: 800–808.
- Fasola G, *et al.* (2007). Low-dose computed tomography screening for lung cancer and pleural mesothelioma in an asbestos-exposed population: baseline results of a prospective, nonrandomized feasibility trial – an Alpe-Adria Thoracic Oncology Multidisciplinary group study (ATOM 002). *Oncologist*; 12: 1215–1224.
- Fedullo PF, *et al.* (2003). The evaluation of suspected pulmonary embolism. *N Engl J Med*; 349: 1247–1256.
- Gruden JF (2005). Thoracic CT performance and interpretation in the multi-detector era. *J Thorac Imaging*; 20: 253–264.
- Heelan RT, *et al.* (1989). Superior sulcus tumors: CT and MR imaging. *Radiology*; 170: 637–641.
- International Early Lung Cancer Action Program Investigators (2006). Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med*; 355: 1763–1771.
- Kalender WA, *et al.* (1990). Spiral volumetric CT with single-breath-hold technique, continuous transport, and continuous scanner rotation. *Radiology*; 176: 181–183.
- Kauczor HU, *et al.* (1996). Normal and abnormal pulmonary ventilation: visualization at hyperpolarized He-3 MR imaging. *Radiology*; 201: 564–568.

- Konen E, *et al.* (2004). Coarctation of the aorta before and after correction: the role of cardiovascular MRI. *AJR Am J Roentgenol*; 182: 1333–1339.
- Kreitner KF, *et al.* (2004). Chronic thromboembolic pulmonary hypertension: pre- and postoperative assessment with breath-hold MR imaging techniques. *Radiology*; 232: 535–543.
- Mabie M, *et al.* (2003). Use and limitations of clinical and radiologic diagnosis of pneumonia. *Semin Respir Infect*; 18: 72–79.
- MacFall JR, *et al.* (1996). Human lung air spaces: potential for MR imaging with hyperpolarized He-3. *Radiology*; 200: 553–558.
- MacMahon H, *et al.* (2017). Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. *Radiology*; 284: 228–243.
- Matoba M, *et al.* (2007). Lung carcinoma: diffusion-weighted MR imaging – preliminary evaluation with apparent diffusion coefficient. *Radiology*; 243: 570–577.
- Mirvis SE, *et al.* (1988). MR imaging of traumatic diaphragmatic rupture. *J Comput Assist Tomogr*; 12: 147–149.
- Müller NL (2002). Computed tomography and magnetic resonance imaging: past, present and future. *Eur Respir J*; 19: Suppl. 35, 3s–12s.
- Müller NL, *et al.* (1992). Value of MR imaging in the evaluation of chronic infiltrative lung diseases: comparison with CT. *AJR Am J Roentgenol*; 158: 1205–1209.
- National Lung Screening Trial Research Team (2011). Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*; 365: 395–409.
- Ost D, *et al.* (2003). The solitary pulmonary nodule. *N Engl J Med*; 348: 2535–2542.
- Padovani B, *et al.* (1993). Chest wall invasion by bronchogenic carcinoma: evaluation with MR imaging. *Radiology*; 187: 33–38.
- Parker MS, *et al.* (2001). Making the transition: the role of helical CT in the evaluation of potentially acute thoracic aortic injuries. *AJR Am J Roentgenol*; 176: 1267–1272.
- Revel MP, *et al.* (2002). Can CT replace bronchoscopy in the detection of the site and cause of bleeding in patients with large or massive hemoptysis? *AJR Am J Roentgenol*; 179: 1217–1224.
- Schoepf UJ, *et al.* (2004). CT angiography for diagnosis of pulmonary embolism: state of the art. *Radiology*; 230: 329–337.
- Tarver RD, *et al.* (2005). Radiology of community-acquired pneumonia. *Radiol Clin North Am*; 43: 497–512.
- Tatli S, *et al.* (2004). CT and MR imaging of the thoracic aorta: current techniques and clinical applications. *Radiol Clin North Am*; 42: 565–585.
- Thieme SF, *et al.* (2008). Dual energy CT for the assessment of lung perfusion – correlation to scintigraphy. *Eur J Radiol*; 68: 369–374.
- Yu H (2011). Management of pleural effusion, empyema, and lung abscess. *Semin Intervent Radiol*; 28: 75–86.

HRCT of the chest

Johny A. Verschakelen

HRCT is a CT acquisition and reconstruction technique that produces highly detailed images. It differs from 'classical' CT by the fact that thin slices (0.5–1 mm) are generated and that high-frequency reconstruction algorithms are used to improve image detail. As thin slices are necessary, the technique is also called thin-slice CT.

HRCT technique

The basic HRCT examination contains continuous axial 0.5–1-mm slices of the entire chest obtained with a multi-slice spiral CT scan at breath-hold after deep inspiration. From these data, additional coronal reconstructions are usually made, as these are not only helpful to study the craniocaudal distribution of disease but often allow better visualisation of the presence and distribution of linear opacities. If desired, these CT data can also be used to calculate maximum intensity projection, which can be helpful to study small lesions and their relationship to the pulmonary lobule, and minimum intensity projection, which may be helpful to study low-attenuation lung disease like pulmonary emphysema. Expiratory HRCT (stopping breathing after deep expiration) should be performed when small airway narrowing is suspected (figure 1). Finally, it may be necessary to add a few slices in the prone body position. These are performed in patients suspected of having early diffuse interstitial lung disease (DILD) when supine CT shows minimal changes in the posterior and basal parts of the lung, areas that are often initially involved in DILD but also often show a gravity-related perfusion increase. Prone CT scans are mostly able to differentiate between these entities as gravity-related changes will disappear in the prone body position. Administration of intravenous contrast is not necessary.

Key points

- HRCT is an imaging technique that offers the highest image detail of the lung parenchyma.
- HRCT is predominantly used to study diffuse interstitial lung diseases but thin-slice CT can be useful in the study of focal lung abnormalities too.
- HRCT of the lungs is an essential element in the multidisciplinary discussion of patients with diffuse interstitial lung diseases.
- HRCT does not replace lung biopsy but helps to decide in which cases a lung biopsy will likely provide more (or important additional) information than CT and in which cases a biopsy is not needed.
- HRCT can be helpful in predicting prognosis and monitoring lung disease progression.

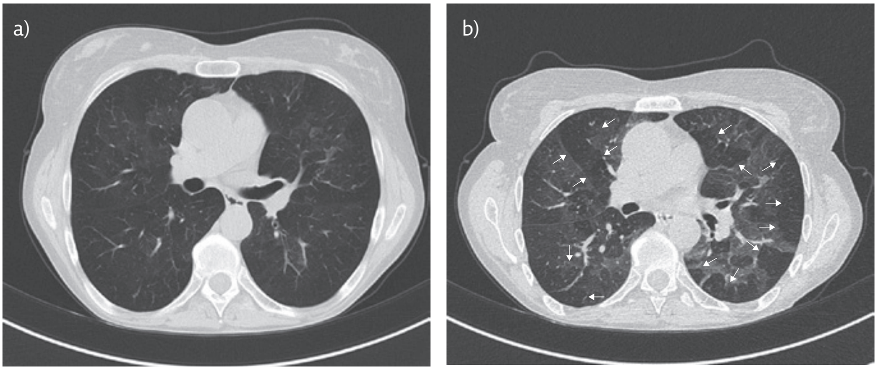


Figure 1. CT after a) deep inspiration and b) deep expiration in a patient with constrictive bronchiolitis. The expiratory CT shows multiple areas of decreased lung attenuation (white arrows) that are hardly visible on inspiratory CT and that are the result of air-trapping caused by small airway narrowing.

HRCT and DILD

Since its introduction into clinical practice, the use of HRCT has constantly increased. This is related not only to the fact that this technique provides important morphological information on the lung parenchyma (it offers the highest imaging detail of the lung) but also because it helps to better understand the clinical and pathological course of some diseases, which has even resulted in the formulation of CT classifications to categorise disease. HRCT is also partly responsible for the radical change in the diagnostic work-up of idiopathic pulmonary fibrosis (IPF). The historical gold standard of histologic diagnosis has been replaced by an integrative approach of clinical, radiological and, when necessary, pathological data during multidisciplinary discussions. Nowadays, HRCT and histology are often considered as ‘silver’ standards. This does not mean that lung biopsy is less important but indicates that the multidisciplinary discussion defines in which case lung biopsy will likely give more (or important additional) information than CT and in which cases biopsy is not needed.

There are several reasons why HRCT plays an important role in this multidisciplinary discussion.

- Some DILDs can have a typical HRCT pattern and when this disease presents with such a pattern, HRCT may be very accurate in the diagnosis, *i.e.* HRCT may have a high positive predictive value (PPV); IPF is one such disease. The PPV of HRCT in IPF patients is >90% when a typical appearance pattern (predominant cystic (honeycombing), irregular linear pattern, traction bronchiectasis and no predominant ground-glass opacity) is combined with a typical distribution pattern (subpleural and basal lung). Unfortunately, this HRCT pattern that strongly suggests IPF is only seen in <50% of cases. In the majority of cases, part of the multidisciplinary discussion will be related to the question of whether the combination of HRCT findings with the clinical data is sufficient for diagnosis or whether an additional lung biopsy is necessary (figure 2). Table 1 gives a list of diseases in which CT can be diagnostic when a typical pattern is present.
- If it is decided that a lung biopsy is necessary, HRCT can help to determine the best location for taking the lung sample by suggesting the most likely areas of active disease and avoiding the areas of (nonspecific) terminal fibrosis.

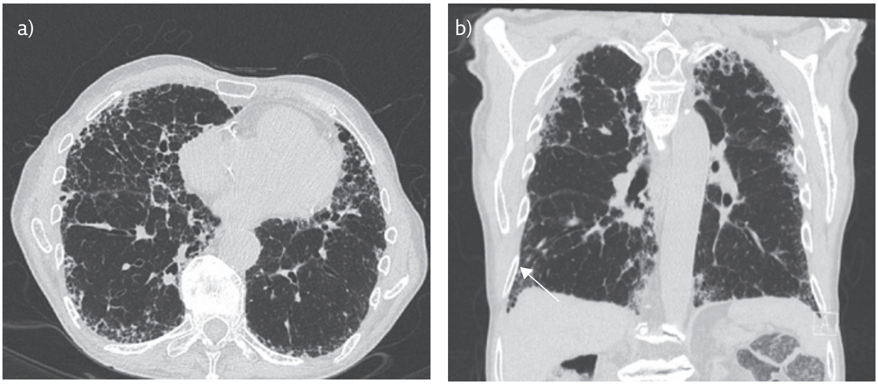


Figure 2. Patient with IPF. CT shows a peripheral subpleural irregular reticular pattern with several traction bronchiectasis. The combination of clinical data and these HRCT findings (probable usual interstitial pneumonia) was considered sufficient for the diagnosis of IPF at the multidisciplinary conference.

- The information provided by HRCT and histology is very often complementary. While histology provides a microscopic view of a small part of the lung, HRCT gives a 'sub-macroscopic' or sub-millimetre view of the entire lung. Combination of this information can indeed result in a single diagnosis. It should be emphasised, however, that in some patients with DILD, multiple pathologic and/or HRCT patterns can be seen simultaneously. In that situation, multidisciplinary discussion should determine the clinical significance of these individual patterns.
- HRCT can be helpful during follow-up of a disease and in this way contributes to the diagnosis by providing information about speed of disease progression. HRCT also plays a role in patients with acute exacerbation of DILD and in the differential diagnosis with infection, left heart failure or other causes of acute lung disease.

HRCT in the diagnosis of DILD

As mentioned earlier, HRCT plays an important role in the process of making the diagnosis of diffuse lung disease. Interpreting a HRCT image of the lungs of a patient suspected of having DILD is a stepwise process. First, it is important to decide whether the lung changes indeed result from a diffuse lung disease, *i.e.* a

Table 1. Diseases that can present with a typical HRCT pattern

IPF
Sarcoidosis
Langerhans cell histiocytosis
Hypersensitivity pneumonitis (figure 3)
Lymphangitic spread of cancer
Silicosis and coal miners' pneumoconiosis
Alveolar proteinosis
Lymphangioleiomyomatosis
Cryptogenic organising pneumonia

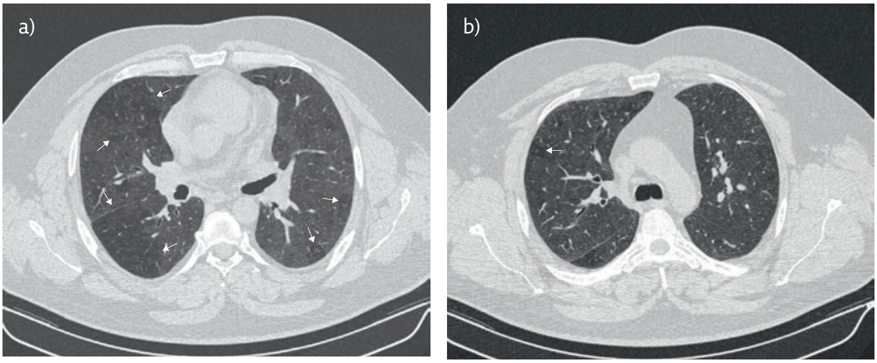


Figure 3. Patient with hypersensitivity pneumonitis. CT shows a diffuse increase in lung attenuation (ground-glass opacity) with several area's of decreased lung attenuation (white arrows). In a non-smoker this presentation is very suggestive for hypersensitivity pneumonitis.

disease that is diffusely spread over an important part of the lung and shows CT changes that are composed in a repeating arrangement (pattern). If it is likely that it is a diffuse lung disease, the disease pattern should be determined: how does the disease appear, *i.e.* what is the appearance pattern (nodular or linear, increased or decreased attenuation) (figure 1), and where are the abnormalities located, *i.e.* what is the distribution pattern (which lung areas are involved and how does disease relate to the pulmonary lobule)? The disease pattern can be very typical (table 1) but is often atypical and a differential diagnosis list should be proposed. In both cases, it is important to have a multidisciplinary discussion in which the HRCT findings are correlated with the clinical findings. HRCT can then be helpful in the decision of whether lung biopsy is or isn't necessary and, if so, of the best site from where to take the biopsy. Finally, the integration of the clinical, HRCT and pathological data may result in an assumed diagnosis or a differential diagnosis list, or the disease may be considered as unclassifiable.

HRCT and predicting prognosis of DILD

Although not absolute, some CT signs can be helpful to predict disease progression and outcome. Ground-glass opacity, lung consolidation and smooth regular thickening of the inter- and intralobular septa suggest more acute and reversible disease while irregular reticulation, honeycombing and lung deformation and destruction suggest irreversible fibrotic lung changes. CT can also depict signs of pulmonary arterial hypertension and early lung cancer which can complicate DILD. In case of acute worsening of disease, CT may help to diagnose pneumonia, pneumothorax or acute exacerbation.

HRCT and monitoring diffuse lung disease

Longitudinal CT scans can provide important information. Accuracy of the initial diagnosis can be increased and disease progression may be depicted. However, although good correlations between CT changes and pulmonary function changes have been reported, visual monitoring of pulmonary involvement in DILD may not always be easy or straightforward. Currently, many automatic and semi-automatic computer-aided diagnosis, quantification and follow-up systems for interstitial lung disease are being developed and tested and it can be expected that these may become important HRCT tools in the diagnosis, management and follow-up of lung disease and DILD in particular.

HRCT and focal lung disease

The introduction of multi-slice spiral CT has made it possible to choose the slice thickness after the examination and in this way highly detailed thin slices of the entire chest can be produced instead of, or in addition to, the thicker slices. So it becomes possible to obtain not only additional detailed information of the focal lung lesion but also of the entire lung. Lymphangitic spread, lung perfusion defects in patients with pulmonary embolism, tumour extension into the surrounding lung, early pulmonary oedema and early small airway infection are examples of disorders that can be better appreciated on thin slices than on thick slices.

Further reading

- De Sadeleer LJ, *et al.* (2018). Diagnostic ability of a dynamic multidisciplinary discussion in interstitial lung diseases: a retrospective observational study of 938 cases. *Chest*; 153: 1416–1423.
- Jacob J, *et al.* (2016). Automated quantitative computed tomography *versus* visual computed tomography scoring in idiopathic pulmonary fibrosis: validation against pulmonary function. *J Thorac Imaging*; 31: 304–311.
- Jacob J, *et al.* (2018). Predicting outcomes in idiopathic pulmonary fibrosis using automated CT analysis. *Am J Respir Crit Care Med*; 198: 767–776.
- Kawel N, *et al.* (2009). Effect of slab thickness on the CT detection of pulmonary nodules: use of sliding thin-slab maximum intensity projection and volume rendering. *Am J Roentgenol*; 192: 1324–1329.
- Lynch DA, *et al.* (2018). Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society white paper. *Lancet Respir Med.*; 6: 138–153.
- Mayo JR (2009). CT evaluation of diffuse infiltrative lung disease: dose considerations and optimal technique. *J Thorac Imaging*; 24: 252–259.
- Nishino M, *et al.* (2010). The spectrum of pulmonary sarcoidosis: variations of high-resolution CT findings and clues for specific diagnosis. *Eur J Radiol*; 73: 66–73.
- Nishino M, *et al.* (2010). Volumetric expiratory HRCT of the lung: clinical applications. *Radiol Clin North Am*; 48: 177–183.
- Quadrelli S, *et al.* (2010). Radiological *versus* histopathological diagnosis of usual interstitial pneumonia in the clinical practice: does it have any survival difference? *Respiration*; 79: 32–37.
- Raghu G, *et al.* (2018). Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*; 198: e44–e68.
- Raj R, *et al.* (2017). Surgical lung biopsy for interstitial lung diseases. *Chest*; 151: 1131–1140.
- Schmidt SL, *et al.* (2009). Diagnosing fibrotic lung disease: when is high-resolution computed tomography sufficient to make a diagnosis of idiopathic pulmonary fibrosis? *Respirology*; 14: 934–939.
- Screaton NJ, *et al.* (2011). The clinical impact of high resolution computed tomography in patients with respiratory disease. *Eur Radiol*; 21: 225–231.
- Sverzellati N, *et al.* (2010). High-resolution computed tomography in the diagnosis and follow-up of idiopathic pulmonary fibrosis. *Radiol Med* 2010; 115: 526–538.

- Travis WD, *et al.* (2013). An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*; 188: 733–748.
- Walsh SL, *et al.* (2014). An integrated clinicoradiological staging system for pulmonary sarcoidosis: a case-cohort study. *Lancet Respir Med*; 2: 123–130.
- Walsh SL, *et al.* (2014). High-resolution CT of interstitial lung disease: a continuous evolution. *Semin Respir Crit Care Med*; 35: 129–144.
- Wells AU, *et al.* (2016). Subclinical interstitial lung abnormalities: toward the early detection of idiopathic pulmonary fibrosis? *Am J Respir Crit Care Med*; 194: 1445–1446.

Nuclear medicine of the lung

Antonio Palla and Duccio Volterrani

Nuclear medicine may contribute to the diagnosis and follow-up of pulmonary embolism; to the diagnosis, follow-up and evaluation of treatment efficacy of pulmonary inflammatory diseases; and to the diagnosis, staging, monitoring of treatment efficacy of lung cancer.

Diagnosis of pulmonary embolism

Thanks to its noninvasiveness, safety and low cost, perfusion lung scintigraphy (PLS) remains a valuable tool for the diagnosis and follow-up of pulmonary embolism. In more detail, PLS has proven useful for:

- Diagnosis of pulmonary embolism
- Detection of pulmonary embolism recurrence under treatment or after treatment discontinuation
- Differential diagnosis between thromboembolic and nonthromboembolic pulmonary hypertension

Two main scintigraphic criteria should be considered for diagnosis:

1) Identification of perfusion defects corresponding to one or more pulmonary segments

2) Diversion of pulmonary blood flow from lower and posterior lung regions where it is most represented in normal subjects

Perfusion defects are typically multiple, wedge-shaped and often bilateral. PLS has a sensitivity of 100% and, thus, the diagnosis of pulmonary embolism may be excluded

Key points

- Nuclear medicine of the lung has a role in the diagnosis and follow-up of pulmonary embolism and inflammatory diseases, and in the diagnosis, staging and treatment monitoring of lung cancer.
- Perfusion scintigraphy is key in the diagnosis and follow-up of pulmonary embolism as it is safe, cheap and noninvasive.
- Gallium-67 scintigraphy and, more recently, positron-emitting radiotracers are useful in detecting and monitoring intrathoracic inflammation and infection.
- 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography is widely used in diagnosis, staging and treatment monitoring of lung cancer.

with certainty when PLS results are normal. The specificity varies in different reported series but on average, does not reach acceptable values. To increase the specificity, ventilation lung scintigraphy (VLS) has been introduced but it is cumbersome, time consuming and poorly available. Nowadays, VLS is only indicated in a limited number of patients with pulmonary embolism. A few years ago, a new classification of perfusion defects was published in order to optimise its diagnostic usefulness in conjunction with chest radiography; this method has made it possible to obtain a diagnostic accuracy similar to that shown by angio-CT. The use of PLS in the diagnostic process should be suggested in patients in whom angio-CT may not be performed due to renal insufficiency, contrast medium allergy, young age and, particularly, female sex. Altogether, these criteria exclude almost 30% of all patients. PLS also plays a leading role in the follow-up of patients with pulmonary embolism, as it helps to monitor the efficacy of treatment in the first few days. Recently, it has allowed prompt detection of early and late pulmonary embolism recurrences and of the evolution towards pulmonary hypertension. Finally, PLS may differentiate between thromboembolic pulmonary hypertension and other types of pulmonary hypertension.

Diagnosis of inflammatory diseases

Gallium-67 citrate binds to multiple iron-binding molecules and has frequently been used to detect infection and inflammation. To acquire images, a scintillation γ-camera with a low-energy collimator is required. Gallium-67 scintigraphy may help with the diagnosis of interstitial lung diseases (ILDs), a group of heterogeneous diffuse parenchymal diseases showing chronic inflammation and fibrosis. Gallium-67 may help in evaluating the activity of connective tissue and of granulomatous disorders, such as sarcoidosis, and fibrosis due to idiopathic pulmonary fibrosis (IPF) and exposure to several drugs may be investigated. In patients with sarcoidosis, this radiotracer shows a high diagnostic sensitivity; in some cases, the typical appearance of 'panda' or 'lambda' signs gives gallium scintigraphy an acceptably high specificity that allows avoidance of the use of invasive diagnostic tests. Moreover, this tracer may help differentiate between sarcoidosis and lymphomas, detect multiple extrapulmonary sites of sarcoidosis or lymphomas, and indicate the proper site for a pulmonary or extrapulmonary biopsy. Conversely, gallium-67 has not been shown to be useful to evaluate the efficacy of steroid treatment in patients with ILDs, since the reduced uptake in response to steroid treatment does not correlate with clinical improvement in patients with IPF. Furthermore, it is currently not known whether a correlation exists between the therapeutic effect of recently discovered antifibrotic drugs, pirfenidone and nintedanib, and the activity of gallium-67. Another potential indication for gallium-67 scintigraphy is the investigation of activity in pulmonary infections and the efficacy of proper therapy. In the diagnostic process for pulmonary tuberculosis, gallium scintigraphy may indicate the necessity for bronchoalveolar lavage and the site where it should be performed. This occurs mostly in cases of suspected re-infection of areas of pleuroparenchymal fibrosis, in cases of suspicion where sputum is repeatedly negative and in immunocompromised patients. Finally, gallium scintigraphy may be of value in lymphomatous diseases in order to differentiate post-radiation induced fibrosis from residual tumour foci when a lung density persists after radiotherapy. Although still employed, gallium-67 has been partly replaced in recent years by the use of positron-emitting tracers, such as Gallium-68 and 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG). Indeed, growing evidence suggests greater advantages from the use of positron-emitting isotopes and of positron emission tomography (PET) in the assessment of diagnosis and efficacy of treatment of the major part of the aforementioned diseases. Gallium-68, a positron-emitting isotope, has similar

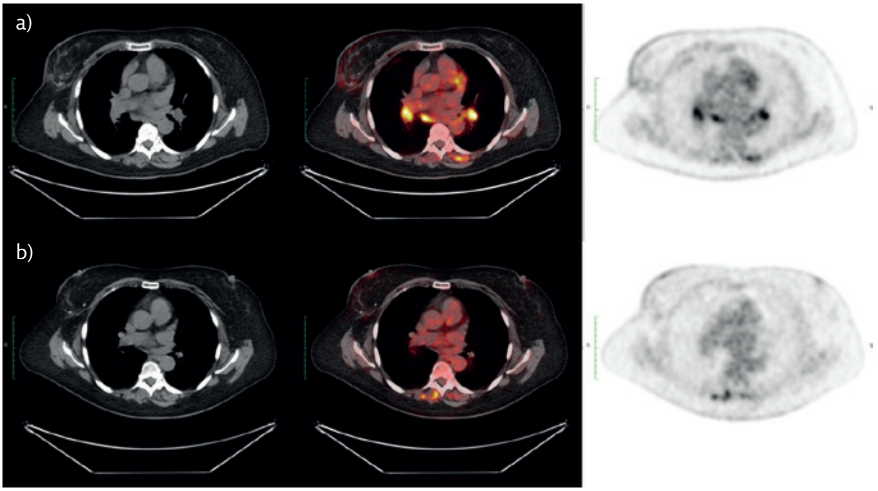


Figure 1. Patient with sarcoidosis. a) Baseline PET/CT shows the presence of several FDG-avid mediastinal and hylar lymph nodes that b) disappear after therapy with corticosteroids (axial images).

characteristics to gallium-67 but also has the advantages inherent to PET imaging. Generally, the indications to the use of gallium-68 are the same as for gallium 67. In sarcoidosis, for instance, gallium-68 scintigraphy may clearly shows improvement under treatment (figure 1). In ILDs, the FDG uptake of gallium-68 has been employed to investigate the diagnosis and the evolution under treatment. Intense FDG uptake in areas of ground glass and honeycombing may reflect an active fibrotic remodelling process. The degree of uptake may also be clinically useful in the evaluation of the efficacy of antifibrotic therapy and patient survival.

Diagnosis of lung cancer

PET is a three-dimensional imaging modality that provides functional or metabolic information. PET/CT systems combine the advantages of PET with those of CT, a high spatial resolution imaging modality; such fusion generally improves diagnostic accuracy by increasing specificity compared with PET alone (figure 2). The most frequently used tracer is FDG, a glucose analogue, the tissue concentration of which is directly related to glucose metabolism. The uptake of FDG may be evaluated by a semiquantitative measurement, the standardised uptake value (SUV), *i.e.* the ratio between the amount of tracer in a specific area and the amount potentially present if the tracer had been evenly distributed in the body.

FDG-PET has proven useful in:

- Diagnosing, staging and restaging lung cancer
- Monitoring the efficacy of treatment
- Defining the biological target volume for radiation treatment planning

A clinically relevant indication of FDG-PET and FDG-PET/CT is the differentiation of benign from malignant solitary pulmonary nodules by replacing invasive modalities of investigation. A SUV of 2.5 has been reported as a guideline for the cut-off between benign (SUV <2.5) and malignant (SUV >2.5) lesions. A meta-analysis from 40 studies showed a sensitivity of 97% but a lower specificity (78%) due to FDG uptake within

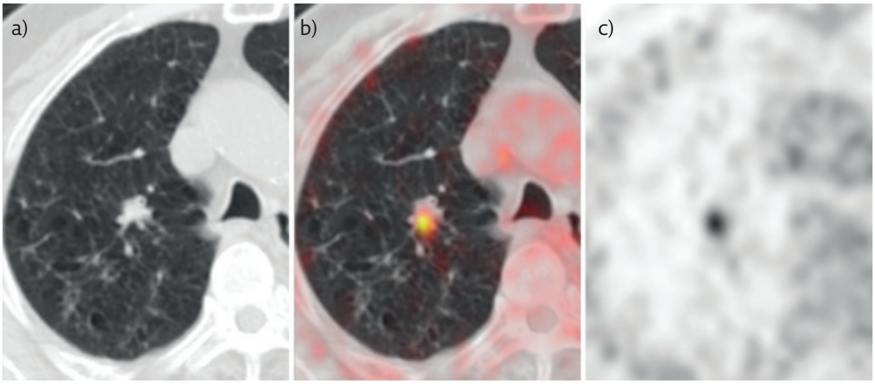


Figure 2. Solitary pulmonary nodule as it appears on a) chest CT, b) PET/CT and c) PET alone.

inflammatory/granulomatous lesions. However, a high rate of false-negative FDG results can occur when nodules are <1 cm (sensitivity of 69% for nodules of 5–8 mm). Moreover, some histotypes, such as bronchoalveolar carcinomas and well-differentiated neuroendocrine tumours, usually present a low glucose metabolic activity and cannot be correctly imaged by FDG PET/CT. The results of a recent meta-analysis suggest that FDG PET/CT in solitary pulmonary nodule evaluation should not be considered as a discriminatory test but rather as a method to be included in a clinical and diagnostic pathway.

FDG-PET/CT is also a standard modality for staging and restaging non-small cell lung cancer. Several studies have demonstrated that FDG-PET/CT is more accurate than CT in the staging of the mediastinum (N state). Due to its high negative predicted value, invasive staging procedures (mediastinoscopy) can be omitted in patients with a negative FDG-PET/CT for mediastinal lymph node involvement. However, recent European Society of Thoracic Surgeons guidelines suggest tissue confirmation with needle aspiration techniques and mediastinoscopy should also be performed in patients with mediastinal FDG-PET/CT negative lymph nodes in cases of cN1, central tumours, peripheral tumours >3 cm and adenocarcinomas with high FDG uptake. A positive finding should not preclude mediastinoscopy.

FDG-PET/CT is useful in disclosing distant metastases (M state) with a high sensitivity and specificity. However, FDG-PET/CT cannot replace CT or MRI for detecting brain metastases.

FDG-PET/CT offers a highly accurate approach for restaging patients with non-small cell lung cancer following surgery, chemoradiotherapy or radiotherapy. A recent meta-analysis that analysed the diagnostic efficacy of FDG-PET/CT compared to other imaging techniques for the detection of recurrent cancer concluded that FDG-PET/CT was a superior modality for the detection of recurrent lung cancer.

FDG-PET/CT provides functional information and metabolic changes that can be detected earlier than morphologic changes. Early changes of FDG-PET/CT SUV during radiotherapy and chemotherapy can predict therapy efficacy. In patients with locally advanced lung cancers who undergo multimodality treatment, correct restaging after induction therapy is needed. FDG-PET/CT is more accurate than contrast-enhanced CT for detecting residual tumour after radiotherapy and chemotherapy (figure 3).

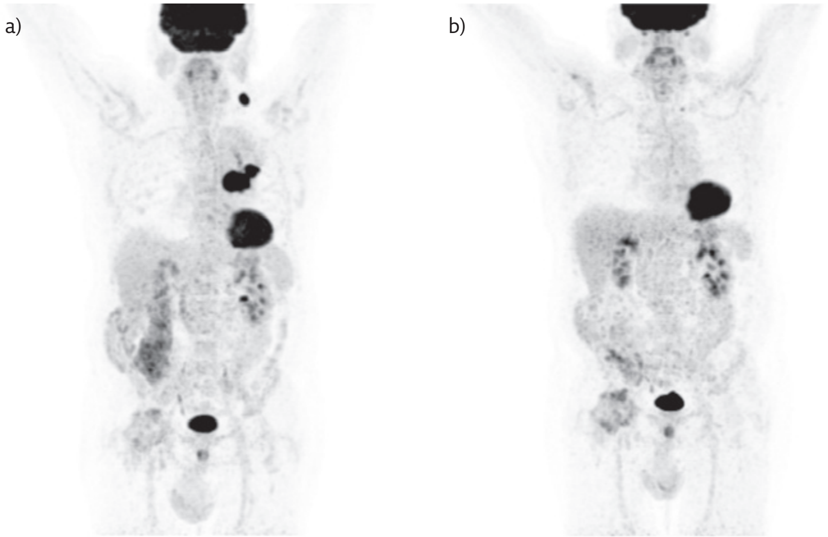


Figure 3. Patient with a non-small cell lung cancer (cT3N3Mx) a) before and b) after neoadjuvant chemotherapy and radiotherapy on the left hilar and left laterocervical nodes. FDG-PET/CT shows the complete regression of the hypermetabolic pulmonary and lymph nodal lesions at the end of treatment.

FDG-PET/CT is useful to define the biological target volume for radiation treatment planning. This approach has the goal of increasing the dose to the tumour and focusing the treatment planning to the biological target that reveals elevated glucose metabolism.

Further reading

- De Leyn P, *et al.* (2014). Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. *Eur J Cardiothorac Surg*; 45: 787–798.
- Divisi D, *et al.* (2018). Diagnostic performance of fluorine-18 fluorodeoxyglucose positron emission tomography in the management of solitary pulmonary nodule: a meta-analysis. *J Thorac Dis*; 10: S779–S789.
- Gopalan D, *et al.* (2017). Diagnosis of chronic thromboembolic pulmonary hypertension. *Eur Respir Rev*; 26: 160108.
- Greenspan BS (2017). Role of PET/CT for precision medicine in lung cancer: perspective of the Society of Nuclear Medicine and Molecular Imaging. *Transl Lung Cancer Res*; 6: 617–620.
- Grijm K, *et al.* (2005). Semiquantitative ^{67}Ga scintigraphy as an indicator of response to and prognosis after corticosteroid treatment in idiopathic interstitial pneumonia. *J Nucl Med*; 46: 1421–1426.
- Groves AM, *et al.* (2009). Idiopathic pulmonary fibrosis and diffuse parenchymal lung disease: implications from initial experience with ^{18}F-FDG PET/CT. *J Nucl Med*; 50: 538–545.
- Kumar V, *et al.* (2013). ^{68}Ga-radiopharmaceuticals for PET imaging of infection and inflammation. *Recent Results Cancer Res*; 194: 189–219.
- Lapa P, *et al.* (2017). Metabolic tumor burden quantified on [^{18}F]FDG PET/CT improves TNM staging of lung cancer patients. *Eur J Nucl Med Mol Imaging*; 44: 2169–2178.

- Palla A, *et al.* (2010). The clinical course of pulmonary embolism patients anticoagulated for 1year: results of a prospective, observational, cohort study. *J Thrombosis and Haemostasis*; 8: 68–74.
- Pesavento R, *et al.* (2017). Impact of residual pulmonary obstruction on the long-term outcome of patients with pulmonary embolism. *Eur Respir J*; 49: 1601980.
- Sostman HD, *et al.* (2008). Sensitivity and specificity of perfusion scintigraphy combined with chest radiography for acute pulmonary embolism in PIOPED II. *J Nucl Med*; 49: 1741–1748.
- Umeda Y, *et al.* (2015). Prognostic value of dual-time-point ^{18}F-FDG PET for idiopathic pulmonary fibrosis. *J Nucl Med*; 56: 1869–1875.
- Weiner R, Hoffer PB, Thakur M. (1981). Lactoferrin: its role as a Ga-67-binding protein in polymorphonuclear leukocytes. *J Nucl Med*; 22: 32–37.

Sputum and exhaled breath analysis

Patrizia Pignatti, Dina Visca, Elisiana Carpagnano, Francesca Cherubino and Antonio Spanevello

Noninvasive techniques such as induced sputum and exhaled breath analysis have proved successful in revealing inflammatory status. These techniques allow longitudinal sampling of inflammatory biomarkers in the lung, providing the possibility of monitoring lung damage process and evaluate treatment strategies in patients with respiratory diseases, including children. Personalised medicine takes advantage of these techniques to better characterise and identify patients to be treated with specific new therapies.

Induced sputum

Induced sputum is one of the most commonly used methods used to determine airway inflammation in asthma, COPD and chronic cough in research and for asthmatic patients in clinical practice limited to specialised centres. The induced sputum technique is a relatively noninvasive method allowing sampling of lower airway secretions from patients who are not able to produce sputum spontaneously.

Procedure

Sputum induction consists of inhalation of ultrasonically nebulised saline solution (isotonic or hypertonic) over different time periods and subsequent expectoration of secretions. The subject is asked to inhale 200 mg salbutamol before induction, and FEV1 is monitored before and after each inhalation to detect possible bronchoconstriction.

After collection, sputum sample is processed within 2 h according to standardised methods with mucolytic agents (dithiothreitol), and centrifugation is required to separate sputum cells from the fluid phase, which is stored at –80°C for soluble mediator evaluation. If mucolytic agents affect the soluble mediators, sputum should be processed with phosphate buffer alone.

Key points

- Sputum and exhaled breath analysis are useful noninvasive tools to appraise airway inflammation, particularly in response to therapy.
- Eosinophils are the most reliable sputum biomarkers for the evaluation of airway inflammation.
- Many inflammatory mediators can be measured in the fluid phase of sputum but their usefulness remains at research level.
- Nitric oxide is the most reliable exhaled biomarker to assess eosinophilic airway inflammation. Other exhaled biomarkers need further validation and a clear demonstration of their utility in the diagnosis and/or follow up of airway diseases.

Safety issues

Sputum induction is a simple, safe and well-tolerated procedure even in patients with severe lung diseases and exacerbations. It is recommended that experienced personnel apply standard operating procedures, taking into consideration the degree of airway obstruction, use a modified protocol for subjects with severe airway obstruction, and assess lung function and symptoms during the procedure. Sputum induction is considered to be safe if the fall in FEV_1 is within 5% of baseline after waiting 15 min. If a FEV_1 fall >20% compared to baseline occurs, the inhalation must be stopped. This adverse effect can affect 11% of patients with asthma or COPD. No safety data are available for subjects with FEV_1 <1L or <50% pred.

Cell counts in different diseases

Sputum samples from healthy subjects are rich in macrophages and neutrophils, and poor in eosinophils, lymphocytes and epithelial cells. The minimum threshold to define eosinophilic airway inflammation varies from 2-3% eosinophils according to various authors and European Respiratory Society (ERS) guidelines.

Asthma is usually characterised by sputum eosinophilia, which predicts a favourable response to corticosteroids. However, noneosinophilic asthma accounts for 25–55% of steroid-naïve asthma patients and is associated with a poor response to corticosteroids.

Sputum is used to characterise airway inflammation as eosinophilic (eosinophils >3%), neutrophilic (neutrophils >61% to >76% according to different studies), mixed (both eosinophilic and neutrophilic) or paucigranulocytic (neither eosinophilic nor neutrophilic). The GINA (Global Initiative for Asthma) document recognises induced sputum as useful in the definition of inflammatory phenotypes, in the evaluation of disease control and in guiding treatment, but highlights that sputum induction is not available in most primary care centres and processing should be performed in specialised laboratories.

In up to 40% of subjects with chronic cough, a sputum eosinophil count of >3% is shown. These subjects with cough, sputum eosinophilia and no lung function alterations receive the diagnosis of eosinophilic bronchitis, and have an objective response to corticosteroid treatment.

In COPD, sputum neutrophils are usually increased and they are associated with reduced FEV_1, suggesting that neutrophilic airway inflammation is functionally relevant. A cut-off for sputum neutrophilia should take age into account, since neutrophils accumulate in the airways with ageing. Sputum eosinophilia may be present in subjects with COPD, and usually predicts higher risk of exacerbations and response to corticosteroid therapy.

Three representative examples of induced sputum are shown in figure 1.

Many inflammatory mediators can be measured in the fluid phase of sputum. These mediators are granulocyte proteins, leakage markers, cytokines and chemokines, eicosanoids, and proteases. Unlike sputum cells, until now, no determination of sputum soluble mediators has entered routine practice for airway inflammation evaluation. Recently, the application of new techniques, such as reverse transcriptase PCR, *in situ* hybridisation, and proteomics, has allowed a wider approach to the study of sputum soluble mediators.

Table 1 summarises cellular and fluid phase markers of airway inflammation in different pulmonary diseases.

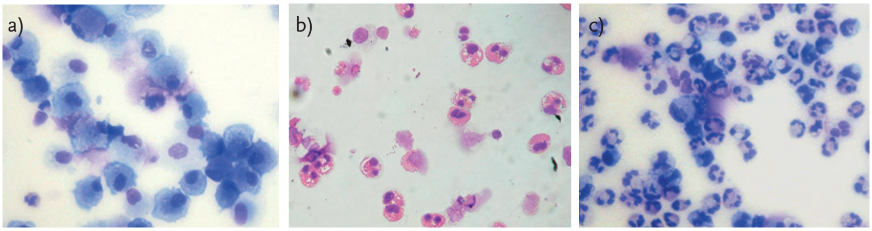


Figure 1. Three representative sputum samples. a) healthy subject with sputum mainly constituted by macrophages. b) asthmatic subject with eosinophilic inflammation. c) COPD subject with neutrophilic inflammation.

Table 1. Biomarkers evaluated in the cellular and fluid phase of induced sputum compared to healthy subjects

Biomarkers[#]	Asthma	COPD	CF	Sarcoidosis
Cellular phase	Eosinophils, neutrophils, CD4$^+$ T-cells, type 2 innate lymphoid cells	Neutrophils, eosinophils, CD8$^+$ T-cells, type 1 innate lymphoid cells	TCC, neutrophils	Lymphocytes, CD4$^+$ T-cells
Fluid phase	ECP, MPO, albumin, fibrinogen, nonkinase plasminogen activator, plasminogen activator, neurokinin A, IL-2, IL-5, IL-6, IL-8, IL-9, IL-12p70, IL-13, Cys-LTs, 8-isoprostane, MMP-9/TIMP ratio, VEGF, IL-17, IL-25, IL-32γ, IL-33, NLRP3 inflammasome, TSLP	IL-1β, IL-8, IL-6, TNF-α, IL-9, IL-10, IL-17, IL-22, IL-23, IL-26, IL-27, IL-32, IL-33, leptin, MPO, HNL, NE, ECP, EPO, LTB_4, GRO-α, MCP-1, GM-CSF, MMP-1, MMP-8, MMP-9, MMP-12, hyaluronan	IL-1β, IL-6, IL-8, IL-13, IL-17, IL-23, NE, TNF-α, TGF-β, IFN-γ, PAR-2, MCP-1	MMP-9, TNF-α, IL-1β, IL-6, IL-17

TCC: total cell count; ECP: eosinophil cationic protein; MPO: myeloperoxidase; IL: interleukin; Cys-LTs: cysteinyl leukotrienes; MMP: matrix metalloproteinase; TIMP: tissue inhibitor of metalloproteinases; VEGF: vascular endothelial growth factor; NLRP3: nucleotide binding oligomerisation domain-like receptor family, pyrin domain-containing 3; TSLP: thymic stromal lymphopoietin; TNF: tumour necrosis factor; HNL: human neutrophil lipocalin; NE: neutrophil elastase; EPO: eosinophil peroxidise; LTB_4: leukotriene-B_4; GRO-α: growth related oncogene-α; MCP-1: monocyte chemotactic protein-1; GM-CSF: granulocyte-macrophage colony-stimulating factor; TGF-β: transforming growth factor β; PAR-2: protease-activated receptor (PAR)-2.
[#]: increased *versus* healthy controls or in different stages/conditions of disease.

Reproducibility and validity

Sputum induction is reproducible and sensitive. A standardised methodology of sputum induction and processing was issued in 2002 by an ERS task force in order to provide guidance for the reproducibility of the results obtained.

Exhaled breath

Measuring biomarkers in breath is useful for monitoring the airway inflammation and oxidative stress that characterises most lung diseases.

Sample collection and analysis

Variable-sized particles or droplets that are aerosolised from the airway lining fluid, distilled water that condenses from the gas phase out of the nearly water-saturated exhalate, and water-soluble volatiles that are exhaled and absorbed into the condensing breath are the main components of exhaled breath condensate (EBC). Recommendations for collection, analysis and future research priorities in exhaled biomarkers have recently been published.

A method called ‘Particles in Exhaled Air’ (PExA) for measuring particles of respiratory tract lining fluid from the small airways has been recently developed.

Exhaled breath analysis is completely noninvasive, safe, and suitable for longitudinal studies and for monitoring the response to pharmacological therapy. Breath analysis consists of direct (on line) or indirect (off line) reading methods, which generally involve collecting and trapping the breath sample, and subsequently transferring it to analytical instruments for analysis.

Direct evaluations include exhaled gas analysis like exhaled nitric oxide fraction (*F*ENO), which is a marker of eosinophilic airway inflammation, carbon monoxide, a marker of inflammation and oxidative stress, and ethane, a marker of lipid peroxidation. For gas analysis, chemiluminescent or electrochemical methods and gas chromatography are the most sensitive methodologies used.

Exhaled breath can be condensed through different cooling devices, resulting in 1–2 mL EBC over 10 min tidal breathing. This procedure is noninvasive, simple and easy to perform in patients of any age. The pH of the EBC has been proposed as an interesting marker to monitor airway inflammation but some concerns exist on deaeration of the EBC sample.

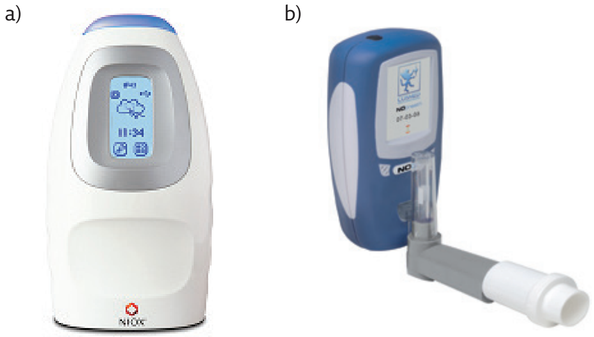


Figure 2. Two commercially available portable F*ENO analysers.*

Recently, increase in exhaled temperature has been considered as a new noninvasive marker of inflamed airways. Validation studies of the exhaled breath temperature (EBT) could support its use in clinical practice. Devices that allow home monitoring of EBT are now available.

Figure 2 shows two commercially available portable *F*ENO analysers.

Biomarkers

Several molecules can be detected in exhaled air of healthy subjects and patients with different inflammatory lung diseases (Table 2).

Table 2. Biomarkers in exhaled breath condensate

Biomarkers	Clinical significance in asthma	Clinical significance in COPD
Eicosanoids and F2-isoprostanes	Increased according to the severity of the disease and the degree of inflammation Assess the effects of pharmacological treatment	Increased according to the severity of the disease and the degree of inflammation
8-isoprostane	Increased	Increased
Leukotrienes	Elevated in both adults and children	
Prostanoids		Elevated in steroid-naïve and in steroid-treated patients Correlates with the degree of airway inflammation
pH	Decreased; normalises with corticosteroid therapy	Decreased Associated with hyperinflation and air trapping
Hydrogen peroxide	Increased in both adults and children Associated with severity and control	Increased in patients with exacerbations
Nitrite/nitrate, nitrosothiol, nitrotyrosine	Increased and correlates with eosinophilic inflammation; reduced by corticosteroid therapy	Increased in early stages of exacerbations
Asymmetric dimethylarginine	Increased	
Malondialdehyde		Increased in subjects with chronic airway disorders
***F*ENO**	Increased; falls after treatment with corticosteroids	Increased during exacerbations; falls after inhaled corticosteroids in stable COPD
Adenosine, ATP, purines	Increased	Increased

Validity

*F*ENO is the most reliable exhaled marker and is used clinically to assess eosinophilic airway inflammation. It is also useful for assessing adherence to inhaled steroid therapy and the need for further anti-inflammatory treatment in asthma. *F*ENO levels scarcely correlate with blood eosinophils, particularly in patients with uncontrolled asthma. *F*ENO predicts the response to inhaled corticosteriods also in patients without asthma, and has proved useful in endotyping severe asthma and identifying responders to biological therapies. Utility of *F*ENO in COPD is less clear since smoking reduces *F*ENO levels, causing misleading results. Nonetheless, high *F*ENO (≥20 ppb) in stable COPD seems to predict patients with higher risk to develop acute exacerbations. Bronchoconstriction reduces *F*ENO levels in both asthma and COPD.

Immunoassays for many EBC biomarkers still need to be validated by reference analytical techniques. Concentrations of markers are often close to the detection limit of the assays, making analytical data less reliable. Dilution of airway lining fluid may influence the results of biomarker analysis in EBC. Standardisation and validation of exhaled breath analysis is important, and special attention should be paid to flow and time dependence, influence of respiratory patterns, origin of markers in EBC, and possible nasal, saliva and sputum contamination. Sensitive and new methodologies (high-pressure liquid chromatography/mass spectrometry, proteomics, metabolomics, genomics, *etc.*) able to define patterns of exhaled biomarkers specific for distinct airway diseases are under evaluation.

Conclusion

Noninvasive methods such as induced sputum and exhaled breath analysis have proved successful in clinical practice and research to study airway inflammation involved in the pathogenesis of respiratory diseases.

Further reading

- American Thoracic Society, *et al.* (2005). ATS/ERS recommendations for standarized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. *Am J Respir Crit Care Med*; 171: 912–930.
- Alcázar-Navarrete B, *et al.* (2018). Persistently elevated exhaled nitric oxide fraction is associated with increased risk of exacerbation in COPD. *Eur Respir J*; 51: 1701457.
- Amer M (2016). Effect of inhaled β2-agonist on exhaled nitric oxide in chronic obstructive pulmonary disease. *PLoS One*; 11: e0157019.
- Barnes PJ, *et al.* (2006). Pulmonary biomarkers in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 174: 6–14.
- Brightling CE (2006). Clinical applications of induced sputum. *Chest*; 129: 1344–1348.
- Carpagnano GE, *et al.* (2017). Validation of the exhaled breath temperature measure: reference values in healthy subjects. *Chest*; 151: 855–860.
- Djukanović R, *et al.* (2002). Standardised methodology of sputum induction and processing. *Eur Respir J*; 20: Suppl. 37, 1s–2s.
- Gao J, *et al.* (2018). Association between fractional exhaled nitric oxide, sputum induction and peripheral blood eosinophil in uncontrolled asthma. *Allergy Asthma Clin Immunol*; 14: 21.
- Haccuria A, *et al.* (2014). Exhaled nitric oxide: a biomarker integrating both lung function and airway inflammation changes. *J Allergy Clin Immunol*; 134: 554–559.

- Horváth I, *et al.* (2005). Exhaled breath condensate: methodological recommendations and unresolved questions. *Eur Respir J*; 26: 523–548.
- Horváth I, *et al.* (2017). A European Respiratory Society technical standard: exhaled biomarkers in lung disease. *Eur Respir J*; 49: 1600965.
- Pizzichini E, *et al.* (1996). Indices of airway inflammation in induced sputum: reproducibility and validity of cell and fluid-phase measurements. *Am J Respir Crit Care Med*; 154: 308–317.
- Price DB, *et al.* (2018). Fractional exhaled nitric oxide as a predictor of response to inhaled corticosteroids in patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility: a randomised controlled trial. *Lancet Respir Med*; 6: 29–39.
- Spanevello A, *et al.* (1997). Induced sputum to assess airway inflammation: a study of reproducibility. *Clin Exp Allergy*; 27: 1138–1144.
- Spanevello A, *et al.* (2000). Induced sputum cellularity. Reference values and distribution in normal volunteers. *Am J Respir Crit Care Med*; 162: 1172–1174.
- Tabatabaian F, *et al.* (2017). Biologic and new therapies in asthma. *Immunol Allergy Clin North Am*; 37: 329–343.

Microbiology testing and interpretation

Margareta Ieven and Veerle Matheeussen

In primary care, microbiological work-up in respiratory infections is primarily meant as an epidemiological investigation in order to guide future empiric antimicrobial policies. Hardly any study has shown that initial microbiological studies in primary care affect the outcome of respiratory infections. Therefore, recent guidelines confirm that microbiological tests such as Gram stains and cultures are not recommended as routine tests in the primary care setting. Nevertheless, an aetiological diagnosis, of both bacteria and viruses and mixtures of these in community-acquired pneumonia (CAP) or lower respiratory tract infections (LRTIs), may be helpful in guiding treatment, particularly in the more severely ill or hospitalised patients. Diagnostic testing should not lead to delays in initiation of therapy, however. Even with extensive diagnostic testing, a specific aetiology is usually identified in only half of all patients, generally at least 1–2 days after the clinical diagnosis is made. With the advent of recently developed rapid techniques, such as immunochromatographic, urinary antigen and particularly nucleic acid amplification (NAA) tests, which produce results within 15 min or 4–5 h, microbiological information is becoming clinically useful (table 1).

Conventional culture techniques

Blood culture

For the diagnosis of pneumonia, blood cultures have a very high specificity but are positive in only about 10–20% of untreated cases. In some studies, a direct correlation has been found between the severity of pneumonia (based on the Fine Severity Index) and blood culture positivity rate. Two sets of blood cultures should be performed in

Key points

For the aetiological diagnosis of lower respiratory tract infections (LRTIs):

- Gram stain and culture of sputum, if of good quality, are valuable in hospitalised patients for the microbiological diagnosis of LRTI caused by *Streptococcus pneumoniae* or *Haemophilus influenzae*.
- Urinary antigen detection is a very helpful and rapid test for the diagnosis of pneumococcal and especially *Legionella* infections.
- Serology is rarely helpful in the management of the individual patient with LRTI.
- Molecular tests for the detection of respiratory viruses and atypical pathogens in specific patient populations are desirable.

Table 1. Diagnostic approach for the most common specific agents in LRTIs

Pathogen	Specimen	Rapid tests	Conventional tests	Comments
Streptococcus pneumoniae	Blood		Blood culture	Positive in 4–18% of cases when collected within 4 days
	Sputum	Gram stain	Culture	Only purulent samples acceptable; can be obtained in 35–40% of patients; informative if >90% Gram-positive diplococci
	BAL, PSB	Gram stain	Culture	Quantitative cultures
	Pleural exudates, TNA	Gram stain	Culture	Very specific; only considered if less invasive methods nondiagnostic
	Respiratory specimens	NAA	Culture	Specificity issues if pneumolysin or autolysin genes are targeted
	Urine	Antigen test		Sensitivity 50–80% of bacteraemic cases; lacks specificity in children
Haemophilus influenzae	Blood		Blood culture	Less frequently positive than for *S. pneumoniae*
	Respiratory specimens	Gram stain	Culture	
	Respiratory specimens	NAA	Culture	Included in some commercial multiplex panels
***Legionella* spp.**	Urine	Antigen test		Sensitivity 66–95%
	Respiratory specimens	NAA	Culture	Culture on appropriate media; late results
	Serum		IgM and IgG serology	Acute and convalescent specimens; retrospective diagnosis
Chlamydophila pneumoniae*, *Mycoplasma pneumoniae	Respiratory specimens	NAA	Culture	Culture on appropriate media; low sensitivity
	Serum		IgM and IgG serology	Acute and convalescent specimens; lack of sensitivity and specificity; not appropriate for individual patient management; retrospective results
Respiratory viruses	Respiratory specimens	Direct antigen tests, NAA	Virus isolation	Requirement for appropriate infrastructure; isolation less sensitive than NAA

BAL: bronchoalveolar lavage; PSB: protected specimen brush; TNA: transthoracic needle aspiration.

all patients with CAP who require hospitalisation; they should be obtained as early as possible in the disease and before any antibiotic treatment is started. Despite their low sensitivity, blood cultures in CAP are considered the gold standard for diagnosis of pneumonia because the organisms are recovered from a normally sterile source. Results may be available after 24–48 h.

Sputum Gram stain and culture

The most frequently submitted specimen in cases of LRTI and, more specifically, in pneumonia is sputum. To be of value for microbial diagnosis and early guidance of therapy, sputum specimens must be representative of lower respiratory secretions and must be interpreted according to strict criteria by an experienced observer. The most widely used method to assess acceptability in this regard is based on cytological criteria. The specimen should therefore be screened by microscopic examination for the relative number of polymorphonuclear cells and squamous epithelial cells in a lower power (10×) field. Invalid specimens (≥10 squamous epithelial cells and ≤25 polymorphonuclear cells per field) should not be examined further. It may be difficult to obtain good-quality, purulent sputum. Many LRTI or pneumonia patients, particularly older ones, do not produce sputum. Satisfactory sputum specimens can be obtained in 32–55% of patients.

Large studies on the diagnostic value of Gram staining in primary care patients are lacking but some hospital-based studies show that in good-quality Gram-stained sputum, the presence of a single or a preponderant morphotype of bacteria (≥90%) may be diagnostic. This is based on correspondence with the organisms recovered from blood cultures obtained in parallel, which are the gold standard. The study by Anevlavis *et al.* (2009) was the first reporting information concerning operating characteristics and the diagnostic value of sputum Gram staining in 1390 patients with bacteraemic CAP. Data from this study suggest that a properly collected and read Gram stain provides a simple, readily available, rapid and inexpensive test result, and can be a dependable test for the early aetiological diagnosis of bacterial pneumonia. Sputum with a mixed flora in the Gram stain has no diagnostic value. The sputum Gram stain is therefore valuable in guiding the processing and interpretation of sputum cultures.

The sensitivity and specificity of sputum cultures are reduced by contamination with flora colonising the upper respiratory tract. The value of sputum cultures in establishing a bacterial cause of LRTI depends on how the specimens are collected and processed. The reported yield of sputum cultures has varied widely, from <20% for outpatients to >90% for hospitalised patients. Sputum culture results are most convincing when the organism(s) isolated in culture are compatible with the morphology of the organisms present in the Gram stain. In the absence of an informative Gram stain, the predictive value of sputum culture is very low.

Rapid antigen tests

Urinary antigen tests

The *Streptococcus pneumoniae* urinary antigen test has been shown to have a sensitivity of 65–85% and a specificity of >90% in adult CAP; however, weak positive results should be interpreted with caution. There is a relationship between the degree of *S. pneumoniae* urinary antigen test positivity and the pneumonia severity index. Therefore, the test could be reserved for high-risk patients for whom conclusive results of a sputum Gram stain are unavailable.

The urinary antigen test may also be applied to pleural fluid and serum samples, with a sensitivity of 50% in bacteraemic patients and 40% in nonbacteraemic patients. The sensitivity of the pleural immunochromatographic test (ICT) is higher than that obtained for blood and pleural fluid cultures, but lower than the detection of pneumococcal antigen in urine samples. However, in some patients with pneumococcal pneumonia and a negative urinary antigen test result, a positive pleural fluid antigen test is detected. The ICT performed on pleural fluid samples therefore augments the standard diagnostic methods of blood and pleural fluid cultures, even in the case of prior antibiotic therapy, and enhances the urinary antigen assay. Vaccination does not result in a positive urinary antigen test. The immunochromatographic urinary antigen test for *S. pneumoniae* is therefore useful for the aetiological diagnosis of severe CAP, especially for patients without demonstrative results of a sputum Gram stain.

Urinary antigen detection is currently the most helpful rapid test for the diagnosis of a *Legionella pneumophila* serogroup 1 infection. Although >50 *Legionella* spp. have been identified, >90% of the isolates associated with legionnaires' disease are *L. pneumophila* and up to 84% of these are *L. pneumophila* serogroup 1. Several test formats have been developed, the enzyme immunoassay (EIA) format being more suited to test a larger number of specimens and taking a few hours to complete. The immunochromatographic format is better suited for single specimens and produces a result within minutes. These tests are particularly useful since culture of *Legionella* spp. is slow and takes 3–4 days. *L. pneumophila* serogroup 1 urinary antigen detection is frequently the first positive laboratory test in this infection. In *L. pneumophila* infection, there is also a relationship between the degree of positivity of the urinary antigen test and the severity of disease: for patients with mild legionnaires' disease, test sensitivities range from only 40% to 50%, whereas for patients with severe legionnaires' disease who need immediate special medical care, sensitivities reach 88–100%.

Antigen tests on pharyngeal specimens

A variety of antigen tests have been evaluated on respiratory specimens. During recent years, a considerable number of previously unknown respiratory viral agents have been discovered whose *in vitro* culture is very slow or even unrealised: human metapneumovirus, the novel coronaviruses NL63 and HKU1, and human bocavirus. Antigens of the many common respiratory viruses (influenza virus, respiratory syncytial virus (RSV), adenovirus and parainfluenza viruses) can be detected by direct immunofluorescence (DIF) or by commercially available EIAs. The sensitivities of these tests vary from 50% to >90% depending on the virus, the patient population studied and the sampling method used. For respiratory infections due to viruses, the optimal specimen is the nasopharyngeal aspirate. Alternatively, oro- or nasopharyngeal swabs can be obtained. For the detection of influenza virus infections, the sensitivity of immunofluorescence can be increased by inoculation of appropriate cells with the clinical sample followed by immunofluorescence after 48 h. Several common respiratory viruses can be detected simultaneously by the use of pooled monoclonal antibodies. The sensitivity and positive predictive value of the DIF test is lower in adults and older people than in children. Rapid methods for the detection of influenza virus are of particular interest because of the availability of antiviral agents that must be given within 48 h of the onset of symptoms.

Serology

Efforts have been made to diagnose infections caused by slowly growing or difficult-to-grow organisms by serology, particularly *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella* infections and respiratory viruses. It should be remembered that the most reliable serologic evidence of an ongoing infection is based on a four-fold increase in the titre of IgG (or IgG and IgM) antibodies during the evolution of the disease episode based on two serum samples collected at an interval of 14–21 days or longer, and/or the appearance of IgM antibodies during the evolution of the disease. IgM tests are usually less sensitive and specific than four-fold changes in antibody titres between paired specimens separated by several weeks. Solitary high IgG titres have no diagnostic meaning for an acute infection, since the moment of the seroconversion is unknown and necessarily took place sometime before the illness under observation started.

The sensitivity and specificity of serological tests are related to the antigen used. For *M. pneumoniae* and *C. pneumoniae*, a great number of antigen preparations have been proposed: whole organisms, protein fractions, glycoprotein fractions and recombinant antigens. Several studies illustrate a lack of standardisation of antigens of *M. pneumoniae*.

For a number of respiratory agents, a variety of tests are available commercially. Some assays lack both sensitivity and specificity, emphasising the need for more validation and quality control.

The serological measurement of specific antibody responses mostly cannot offer an early diagnosis and, therefore, has limited application for an aetiological diagnosis and the routine management of the individual patient with LRTI. Consequently, it is an epidemiological, rather than a diagnostic, tool.

Nucleic acid amplification tests

The newest approach in the diagnosis of respiratory tract infections is the detection of microbial nucleic acids by NAA tests. Culture procedures for viruses and fastidious bacteria (*M. pneumoniae, C. pneumoniae, L. pneumophila* and *Bordetella pertussis*), are too insensitive and too slow to be therapeutically relevant, and these pathogens therefore should be detected using NAA tests, whose sensitivity is almost always superior to that of the traditional procedures.

A multitude of reports has appeared on the epidemiology of LRTIs but most are restricted to a few viruses (influenza, sometimes together with RSV, and rhino-, metapneumo- or coronaviruses) and/or to some population groups, *e.g.* children, adults or the elderly. Great variations occur as a function of time, place and the age-groups studied as well as in the diagnostic gold standard test used, varying between viral culture and serology. Although the role of some new viruses is becoming clearer in specific patient populations, more studies are needed to identify the clinical relevance of some others, such as the bocavirus. All these studies were performed with traditional NAA tests that require at least 1–2 days, producing *a posteriori* results that were unavailable to the clinician in time to have an impact on patient management. Real-time multiplex NAA tests offer a solution. To cover the wide spectrum of aetiological respiratory agents, a number of uni- and/or multiplex reactions are performed simultaneously. Both in-house and commercially available multiplex NAA tests for the simultaneous detection of two, three or up to 22 different respiratory pathogens, including the 'atypical' *M. pneumoniae*, *C. pneumoniae* and *L. pneumophila*, and respiratory viruses, with a mixture of primers, have been developed.

The use of single-target or multiplex assays combined with traditional bacteriological techniques has increased the diagnostic yield in respiratory infections by 30–50%

compared with the traditional techniques alone. When these NAA tests are combined with traditional bacteriological techniques to diagnose *S. pneumoniae* infections, >50% (and in some studies of CAP up to 70%) of aetiological agents can be detected.

The wider application of multiplex reactions during recent years has resulted in the detection of numerous simultaneous viral infections with widely varying incidences: from 3% to even 23% or 35%, depending on whether bacterial agents are also included. The divergent incidences may result from the variety of diagnostic panels applied. Combined viral and viral–bacterial infections are diagnosed but no preferential combinations have been found. The clinical significance of combined infections remains to be further clarified. Respiratory viruses have also been increasingly recognised as causes of severe LRTIs in immunocompromised hosts. Respiratory infections are more common in solid organ recipients, particularly in lung transplant recipients. Infections are especially dangerous prior to engraftment and during the 3 months after transplantation, in the setting of graft *versus* host disease. The origin of the infections is community-acquired as well as nosocomial.

As more epidemiological information on the role of a panel of respiratory viral pathogens becomes available, it is clear that screening for these viruses in specific patient populations, such as transplant patients, very young children or the elderly, is desirable, and preventive and therapeutic recommendations may take this information into account.

NAA tests are, however, not required for every purpose. For cohorting RSV-infected paediatric patients, the DIF tests can be as sensitive as a NAA test and the results are available within 60 min (and at lower cost than with NAA tests). Very rapid chromatographic tests are also available for RSV, which can be performed in the laboratory outside virology laboratory operating hours. However, these tests lack sensitivity when applied to respiratory samples of adult patients.

Conclusion

In recent years, significant progress has been made in the microbiological diagnosis of respiratory infections. A straightforward interpretation of a good-quality, Gram-stained sputum sample has been established, and has been shown to be important for rapid diagnosis of pneumonia and the interpretation of culture results in severely ill patients.

The number of possible aetiological agents (viruses and fastidious bacteria) has been extended, and their epidemiology has been clarified. Sensitive and rapid methods for their detection have been developed and are increasingly validated in clinical settings.

Amplification techniques are, at present, more expensive than conventional approaches. However, improvements in standardisation and automation for sample preparation, and other technical advances, will lead to increased use of amplification methods and cost reductions to rates competitive with conventional methods. Several studies have tended to show cost efficiency of rapid diagnosis of acute respiratory infections resulting from reduced antibiotic use and complementary laboratory investigations, but most significantly from shorter hospitalisation and reduced isolation periods. Serological diagnosis of those cases that remain undetected by the NAA tests is of no clinical use, as it is available only after many days or even weeks.

Further reading

- Anevlavis S, *et al.* (2009). A prospective study of the diagnostic utility of sputum Gram stain in pneumonia. *J Infect*; 59: 83–89.
- Buller RS (2013). Molecular detection of respiratory viruses. *Clin Lab Med*; 33: 439–460.
- Ieven M (2007). Currently used nucleic acid amplification tests for the detection of viruses and atypicals in acute respiratory infections. *J Clin Virol*; 40: 259–276.
- Ieven M (2008). Microbiological diagnosis of community-acquired pneumonia. *In*: Torres A, Menéndez R, eds. Community-Acquired Pneumonia: Strategies for Management. Chichester, John Wiley and Sons Ltd; pp. 43–61.
- Ieven M, *et al.* (2018). Aetiology of lower respiratory tract infection in adults in primary care: a prospective study in 11 European countries. *Clin Microbiol Infect*; 24: 1158–1163.
- Loens K, *et al.* (2009). Optimal sampling sites and methods for detection of pathogens possibly causing community-acquired lower respiratory tract infections. *J Clin Microbiol*; 47: 21–31.
- Loens K, *et al.* (2016). *Mycoplasma pneumonia*: current knowledge on nucleic acid amplification techniques and serological diagnostics. *Front Microbiol*; 7: 448.
- Mahony JB (2008). Detection of respiratory viruses by molecular methods. *Clin Microbiol Rev*; 21: 716–747.
- Murdoch DR (2016). How recent advances in molecular tests could impact the diagnosis of pneumonia. *Expert Rev Mol Diagn*; 16: 533–540.
- Sinclair A, *et al.* (2013). Systematic review and meta-analysis of urine-based pneumococcal antigen test for diagnosis of community-acquired pneumonia caused by *Streptococcus pneumoniae*. *J Clin Microbiol*; 51: 2303–2310.
- Templeton KE, *et al.* (2005). Improved diagnosis of the etiology of community-acquired pneumonia with real-time polymerase chain reaction. *Clin Infect Dis*; 41: 345–351.
- Woodhead M, *et al.* (2011). Guidelines for the management of adult lower respiratory tract infections. *Clin Microbiol Infect*; 17: Suppl. 6, E1–E59.

Laboratory diagnosis of mycobacterial infections

Claudio Piersimoni

Although the prevalence of TB in industrialised countries is low, one thing remains certain, TB, including multidrug-resistant (MDR) and extensively drug-resistant (XDR)-TB, is no longer restricted to low income countries. In addition, many species of nontuberculous mycobacteria (NTM) are now recognised as a cause of pulmonary disease in man with increasing frequency.

The rapid and accurate diagnosis of TB is of the utmost importance; it involves the isolation and identification of the aetiological agent, *Mycobacterium tuberculosis* complex (MTC), while design of an appropriate therapeutic regimen relies on the results of anti-TB drug susceptibility testing (DST).

Laboratory services are an essential component of effective TB control and elimination. Unfortunately, they are at the end of decision tree for the patient's health improvement; thus, they are unable to prevent delays in diagnosis related to both the patient and the physician.

Seven tests performed in clinical microbiological laboratories are recommended for TB control and elimination:

- microscopy for acid-fast bacilli (AFB)
- nucleic acid amplification (NAA)
- AFB detection by culture
- identification of cultured mycobacteria
- molecular detection of drug resistance
- DST for first-line drugs
- DST for second-line drugs

Key points

- Think of TB; if you do not, the laboratory cannot help you.
- Do not use microbiological tests as screening tests.
- Remember that the best way to improve test sensitivity is to submit high-quality specimens.
- Molecular tests cannot replace conventional culture.
- If your laboratory does not meet current quality standards (testing and turnaround times), refer your specimens to a larger laboratory.

These tests should not only be available to every clinician involved in TB diagnosis and management but also be available in a timely manner according to well-defined turnaround times.

Specimen procurement, transport and processing

Success in detecting and isolating mycobacteria strongly depends on the following principles.

1) Select patients soundly suspected of having an active disease.
2) Submit appropriate specimens, collected from the body sites most likely to yield mycobacteria. Inappropriate or redundant specimens must be discouraged.
3) Ensure that adequate volumes of samples are properly collected, stored and delivered to the laboratory.

Most clinical specimens contain an abundance of nonmycobacterial organisms. Unless an attempt is made to get rid of such contaminants, they will easily suppress the slow growth of mycobacteria. This key procedure is referred to as ‘decontamination’, and is usually performed using sodium hydroxide at a concentration mild enough to kill contaminants without damaging mycobacteria.

Microscopy

The first step in the laboratory diagnosis of TB is microscopic examination of specimen smears stained using an acid-fast procedure. Microscopy is rapid, easy and inexpensive, providing the physician with a presumptive diagnosis of TB and a simultaneous assessment of the patient’s infectiousness.

Since the sensitivity of microscopy is relatively low, requiring 10^3–10^4 bacilli per mL of specimen to allow detection, smears should always be prepared from concentrated specimens. The acid-fast staining procedure depends on the ability of mycobacteria to retain dye when treated with acid or acid–alcohol solution. Two types of acid-fast stains are commonly used:

- the carbol fuchsin stain, which includes the Ziehl–Neelsen and Kinyoun methods; and
- a fluorochrome procedure using auramine O or auramine–rhodamine dyes.

The latter provides a 10% more sensitive performance and also permits faster screening of smears. In this context, an important advance in smear microscopy is the adaptation of light-emitting diode (LED) technology to specimens stained with fluorescent dyes. Microscopes using LEDs as a light source are durable and low-cost and do not have any of the disadvantages featured by conventional fluorescent microscopes.

AFB seen on smear may represent either MTC or NTM. However, because of the infectious potential of MTC, sputum smear microscopy should be performed within one working day of specimen reception and positive results should be reported immediately by telephone, fax or other electronic means, as soon as they are available.

Molecular detection of MTC

With the purpose of obtaining faster results and a more accurate diagnosis of TB than those achievable with microscopy and liquid culture, several molecular methods were introduced and have been evaluated worldwide.

These technologies allow for the amplification of specific target sequences that can be detected through the use of a complementary nucleic acid probe.

Although many in-house amplification methods have been described in published studies, most amplification tests currently used in clinical laboratories are supplied commercially. While these assays have demonstrated an excellent specificity, their sensitivity cannot equal that of culture-based methods, especially for smear-negative samples. In a recent meta-analysis, pooled sensitivities and specificities of 85% and 97%, respectively, were reported.

NAA methods can be applied to decontaminated respiratory specimens within hours, producing a positive result with as few as 10^2 bacilli per mL of specimen. They should be performed within 48 h of specimen receipt. NAA tests are regularly applied to smear-positive respiratory samples to provide rapid confirmation that the infecting mycobacteria belong to the MTC. Since the clinical utility of NAA tests is for ruling in active TB, it is of utmost important that they are employed on the basis of a sound clinical suspicion. Routine implementation of NAA testing without consideration of clinical data lacks cost-effectiveness and may be misleading.

Culture

All clinical specimens suspected of containing mycobacteria should be inoculated onto culture media for the following reasons.

- Culture is the most sensitive method, being able to detect as few as 10 mycobacteria per mL of specimen.
- Growth of the organisms is necessary for proper species identification.
- DST requires culture of the organism.
- Genotyping of the cultured strain may be useful to study clusters of TB cases.

Three different types of culture media are currently available: egg-based (Löwestein–Jensen), agar-based (Middlebrook 7H10 or 7H11 medium) and liquid (Middlebrook 7H9 and other 7H9-based commercial broths), whose selectivity may be greatly improved by adding antibiotics. A combination of liquid and solid culture gives the most rapid and optimal rates of mycobacterial recovery from clinical specimens.

Among liquid media, automated culture systems have been developed that are continuously monitored and also able to perform DST.

Identification

The genus *Mycobacterium* consists of >170 different species, all of which appear similar on acid-fast staining. More than two-thirds of them, both saprophytes and (potential) pathogens, may be recovered from human sources.

Causative agents of TB in humans (*M. tuberculosis*, *Mycobacterium bovis*, *M. bovis* bacille Calmette–Guérin (BCG), *Mycobacterium africanum*, *Mycobacterium caprae*, *Mycobacterium microti*, *Mycobacterium pinnipedii* and *Mycobacterium canettii*) are referred to as MTC and most clinical laboratories identify these organisms only to the level of the complex. This practice is supported by two rapid identification procedures that, based on distinctive molecular and antigenic characteristics of the MTC, have gained widespread use:

- nucleic acid hybridisation
- immunochromatographic assay

Table 1. Turnaround times for essential laboratory tests recommended by the American Thoracic Society to provide effective TB control and elimination

Test	Maximum turnaround time
Microscopy for AFB	≤24 h from receipt by laboratory
NAA assay	≤48 h from date of specimen collection
Mycobacterial growth detection by culture	≤14 days from date of specimen collection
Identification of cultured mycobacteria	≤21 days from date of specimen collection
DST	
First-line drugs	≤30 days from date of specimen collection
Second-line drugs	≤4 weeks from date of request

Reproduced and modified from American Thoracic Society *et al.* (2005) *Am J Respir Crit Care Med*; 172: 1169–1227, with permission from the publisher.

It is recommended that laboratories culture and identify MTC within 21 days of receiving the patient's specimen (table 1). This goal can be obtained only by combining liquid culture with the above rapid identification methods.

In addition, mycobacteria other than MTC may be identified using specific probes, DNA sequencing and most recently mass spectrometry (matrix-assisted laser desorption ionisation time-of-flight (MALDI-TOF) technology).

Drug susceptibility testing

DST should be performed on the initial isolate from all new TB cases. In addition, it should be repeated if the patient continues to be culture-positive after 2–3 months of treatment or exhibits positive culture after a period of negative cultures.

The source for DST may be either a smear-positive specimen (direct method) or, most often, growth is first isolated in pure culture from clinical specimens and then inoculated into a drug-containing medium (indirect method). Growth of mycobacteria in the presence of the drug(s) is then compared with a drug-free control.

Among different DST methods, the proportion method is the most widely used. It allows determination of the proportion of MTC organisms that are resistant to a given drug at a single (critical) concentration. The susceptibility proportion was set at 1%, because higher proportions of drug-resistant bacilli were shown to be associated with treatment failure. The critical concentration of a drug is the level of drug that inhibits the growth of most organisms within the population of a wild-type strain without affecting the growth of strains recovered from clinically resistant patients.

Results of the first-line drugs assay (isoniazid, rifampicin, ethambutol and pyrazinamide) should be reported within 4 weeks from specimen receipt. Although agar proportion is currently the reference method, two commercially available automated systems (BACTEC MGIT 960 (BD, Franklin Lakes, NJ, USA) and ESP culture system (Thermo Scientific, East Grinstead, UK)) have been cleared for susceptibility testing of first-line drugs. The use of these liquid systems has not yet been approved for susceptibility testing of second-line drugs (amikacin, capreomycin, ethionamide, kanamycin, moxifloxacin, para-aminosalicylic acid, rifabutin, streptomycin and linezolid), which still relies on the agar proportion method.

Compared to other laboratory tests, accuracy is much more important than speed in the case of drug susceptibility. Thus, results should come from a small number of well-equipped, experienced laboratories enrolled in a national and/or supranational DST quality control scheme.

Molecular detection of resistance

Although detection of drug resistance in MTC has traditionally been accomplished by culture-based assays, the emergence of MDR- and XDR-TB demands improved and faster detection methods. In this context, several molecular approaches have been developed aimed at detecting gene mutations known to be associated with phenotypic resistance to a particular drug.

As DNA sequencing (the reference method to look for specific mutations) would be problematic for most diagnostic laboratories, simpler procedures such as the line probe assay (LiPA) have recently been introduced. It relies on the reverse hybridisation of oligonucleotides on plastic strips to which specific probes have been immobilised. Amplified target sequences from the strain under evaluation are bound to the probes and hybridisation is revealed by the development of a coloured line on the strip.

There are currently three commercially available LiPAs for the rapid detection of drug resistance in MTC: the INNO-LiPA Rif TB (Innogenetics, Ghent, Belgium) for detecting resistance to rifampicin; the GenoType MTBDR*Plus* (Hain Lifesciences, Nehren, Germany) for the simultaneous detection of resistance to rifampicin and isoniazid; and the GenoType MTBDR*sl* (Hain Lifesciences), which detects the most frequent mutations associated with resistance to fluoroquinolones, aminoglycosides and ethambutol. These tests are validated for use in cultured strains as well as in smear-positive respiratory samples.

Real-time PCR technology has also been proposed for the rapid detection of drug resistance in MTC. Different assays have been developed, which include the XpertMTB/RIF (GeneXpert system; Cepheid, Maurens-Scopont, France), an automated molecular test for simultaneous detection of MTC and rifampicin resistance. This cartridge-based NAA assay employs a hemi-nested real-time PCR and requires just a single manual step with minimal sample manipulation. The remaining analysis is performed by the GeneXpert instrument, relatively rapidly (~2 h). Clinical validation trials performed in low-incidence settings with a prevalence of paucibacillary disease and full mycobacteriology capabilities showed a good diagnostic accuracy. Although the results for smear-positive samples were within the range observed in high-incidence settings, sensitivity of the XpertMTB/RIF assay for smear-negative samples was found to be comparable to that of other commercial assays. Similarly, false-positive results of rifampicin resistance were observed in settings characterised by a low prevalence of resistance.

To overcome this drawback, the new Xpert Ultra assay has recently been introduced as an alternative to Xpert MTB/RIF. Recent evaluations of Xpert Ultra suggest that it offers improved sensitivity compared to Xpert MTB/RIF in smear-negative TB and HIV-associated TB meningitis. However, the improved sensitivity may be associated with a reduction in specificity which requires further evaluation. Xpert assays may complement the current reference standard of TB diagnostics, and increase its overall sensitivity and speed. Further studies are required to determine the optimal level of the healthcare system where this system can be used cost-effectively.

Finally, whole-genome sequencing is a recently introduced molecular technique that enables the screening of known resistance-associated mutations, while also providing opportunities to detect and characterise other mutations whose role in predicting resistance is still undefined.

Organisation of laboratory services

Any TB laboratory-based diagnostic procedure should be performed by appropriately trained staff working to standardised operating procedures in appropriately equipped and safe laboratories, to well-defined national and international proficiency and quality standards. In this context, mycobacteriology laboratory consolidation at the regional level is strongly recommended.

Further reading

- Centers for Disease Control and Prevention (2009). Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. *MMWR Morb Mortal Wkly Rep*; 58: 7–10.
- Clinical and Laboratory Standard Institute (2018). Laboratory Detection and Identification of Mycobacteria. 2nd Edn. M48. Wayne, CLSI.
- Clinical and Laboratory Standard Institute (2018). Susceptibility Testing of Mycobacteria, Nocardiae, and other Aerobic Actinomycetes. 3rd Edn. M24. Wayne, CLSI.
- Davies PDO, *et al*. (2008). The diagnosis and misdiagnosis of tuberculosis. *Int J Tuberc Lung Dis*; 12: 1226–1234.
- Dorman S (2015). Advances in the diagnosis of tuberculosis: current status and future prospects. *Int J Tuber Lung Dis*; 19: 504–516.
- Dorman SE, *et al*. (2017). Xpert MTB/RIF Ultra for detection of *Mycobacterium tuberculosis* and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *Lancet Infect Dis*; 18: 76–84.
- European Centre for Disease Prevention and Control (2011). Mastering the Basics of TB Control: Development of a Handbook on TB Diagnostic Methods. Stockholm, ECDC.
- Forbes BA, *et al*. (2018). Practice guidelines for clinical microbiology laboratories: Mycobacteria. *Clin Microbiol Rev*; 31: e00038-17.
- Lewinsohn DM, *et al*. (2017). Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. *Clin Infect Dis*; 64: e1–e33.
- Ling DI, *et al*. (2008). Commercial nucleic-acid amplification tests for diagnosis of pulmonary tuberculosis in respiratory specimens: meta-analysis and meta-regression. *PLoS One*; 3: e1536.
- Palomino JC (2009). Molecular detection, identification and drug resistance detection in *Mycobacterium tuberculosis*. *FEMS Immunol Med Microbiol*; 56: 103–111.
- Tenover FC, *et al*. (1993). The resurgence of tuberculosis: is your laboratory ready? *J Clin Microbiol*; 31: 767–770.
- Weyer K, *et al*. (2013). Rapid molecular TB diagnosis: evidence, policy-making and global implementation of XpertMTB/RIF. *Eur Respir J*; 42: 252–271.

Biopsy

Stefano Gasparini

A wide range of biopsy techniques is available in clinical practice to obtain cytohistological tissue in cases of localised lesions such as consolidation, nodules/masses or infiltrates. Biopsy strategy should be evaluated based on the target and its relationship with the bronchial tree. The choice of sampling approach mostly depends on the location of the lesion, which might be 'central' endobronchial (*i.e.* directly visible through flexible bronchoscope), peripheral or located in the hilar–mediastinal area. A careful evaluation of the CT scan, which must be always available before biopsy, leads to a proper assessment of the location of the lesion.

Central endobronchial lesions

Forceps biopsy, brushing, washing and transbronchial needles are currently the sampling tools available to approach central endobronchial lesions. Forceps biopsy is usually the preferred option, as meta-analyses of data documented a sensitivity ranging from 74% to 80% in this setting, including several studies reporting values even higher than 90%.

Key points

- For central endobronchial lesions (in the visible range of bronchoscopy), biopsy forceps are the recommended sampling instrument as they provide better sensitivity. A transbronchial needle can be useful in case of intramural or peribronchial lesions.
- Peripheral pulmonary lesions (PPLs) can be approached both transbronchially and percutaneously. For the transbronchial approach to PPLs, a guidance system (fluoroscopy, ultrasound miniprobe or electromagnetic navigation bronchoscopy) should be available.
- Percutaneous needle biopsy of PPLs provides better sensitivity than the transbronchial approach but the higher incidence of complications (pneumothorax) suggests the use of transthoracic biopsy when bronchoscopy fails to obtain a diagnosis.
- For lesions localised outside the tracheobronchial wall (hilar–mediastinal area), the use of transbronchial needle aspiration (TBNA) is mandatory. TBNA under ultrasound guidance with the use of an echobronchoscope (EBUS-TBNA) increases the diagnostic yield of TBNA and allows complete mediastinal staging of lung cancer.

Brushing and washing are sampling techniques that are widely used to collect cytological tissue from bronchoscopically visible lesions of the airways. However, the diagnostic yields of brushing and washing are lower than those of forceps biopsy: the sensitivities of brushing and washing range from 59% to 72% and from 29 to 76%, respectively. Furthermore, there is no strong evidence on the adequacy of these methods for molecular evaluation in cases of lung cancer.

Another valuable and largely diffuse tool for sampling central airway lesions is transbronchial needle aspiration (TBNA). In bronchoscopically visible lesions, TBNA offers the advantage of penetrating the deep layers of the mucosa and the peribronchial area, allowing access to pathological processes with the intraparietal or submucosal component. The sensitivity of TBNA for central bronchial lesions does not significantly differ from that of forceps biopsy, ranging from 68% to 91%. In several studies, the use of TBNA in addition to biopsy for central lesions has significantly increased the diagnostic success. However, no large prospective studies focused on cost-effectiveness of this combination are yet available, and thus, the routine use of TBNA along with biopsy cannot be justified in all central airway lesions due to cost.

Recently, cryobiopsy was introduced into clinical practice, especially for diffuse lung diseases. A multicentre study demonstrated better sensitivity of cryobiopsy for central endobronchial lesions in comparison to traditional forceps biopsy (95% *versus* 85.1%) without differences in the complication rate. However, cryobiopsy requires intubation and its use cannot be suggested in the clinical routine, but it could be a useful tool for difficult lesions or after a first unsuccessful attempt.

Peripheral lesions

Peripheral pulmonary lesions (PPLs) (nodules, masses or infiltrates) localised outside the direct vision of the flexible bronchoscope can be sampled both transbronchially or percutaneously. The transbronchial approach to PPLs can be performed using different sampling instruments: forceps biopsy, transbronchial needles, brushing or curette. Whatever sampling instrument is employed, the use of a guidance system is mandatory, as it allows assurance that biopsy is performed in the target lesion. Fluoroscopy with a rotating C-arm is the most widely adopted guidance system. In recent years, new technologies have been introduced to guide the sample in PPLs (virtual bronchoscopy, ultrasound miniprobe and electromagnetic navigation bronchoscopy). Even though some systematic reviews have shown better sensitivity of these new systems in comparison to fluoroscopy, especially for small PPLs, no large randomised studies have been performed to demonstrate the real advantage of the new guidance tools in comparison to fluoroscopy. In the absence of a guidance system, in cases of localised peripheral tumours, bronchoalveolar lavage is generally performed but its sensitivity is usually poor (<10%).

The sensitivity of the transbronchial approach to PPLs under fluoroscopic guidance is highly heterogeneous, as it ranges from 22% to 83% with a mean value of 78%. Factors able to influence the diagnostic success of the procedure include the size of the lesion, the type and the number of the sampling instruments employed, the distance of the target from the hilum, and the relationship between the lesion and the airways. The presence of a ‘bronchus sign’ (*i.e.* CT scan evidence of a bronchus leading to or contained within the lesion) is the best predictor of a diagnostic transbronchial approach to PPLs, whatever guidance system is used.

There is evidence that transbronchial needles increase sensitivity in malignant lesions in comparison to that obtained with forceps biopsy or brushing, as the needle allows penetration of lesions that do not involve the surface of the mucosa.

PPLs can also be approached by percutaneous needle aspiration (PCNA)/biopsy. The most common guidance system for PCNA is CT but biplane fluoroscopy and external ultrasound (when the lesion is in contact with the chest wall) can also be used. Commercially available needles are either aspiration needles or histology needles that yield a tissue core. The use of a histology needle is preferred since it allows acquisition of histological material that is better for molecular evaluation of some biological markers (*e.g.* PD-L1), which is needed for the personalised treatment of lung cancer. The reported sensitivity of PCNA, ranging from 60% to 97%, is higher than with the transbronchial approach, but the incidence of complications is greater, with an incidence of pneumothorax around 25%. For this reason, PCNA should be reserved when the transbronchial approach fails to obtain a diagnosis.

Lesions located outside the airways: the hilar–mediastinal region

TBNA is currently the only technique that permits sampling of cytohistological material from lymph nodes or from pathological processes located in the hilar–mediastinal region. 'Conventional' TBNA, performed without the echobronchoscope, demonstrates good sensitivity (78%), especially if the pathological process is >2 cm and located in the right paratracheal or subcarinal area. However, in recent years, the use of TBNA under ultrasonographic guidance through an echobronchoscope (EBUS-TBNA) has greatly improved the bronchoscopic approach to hilar–mediastinal pathological processes, providing a sensitivity >90% and an accurate method for lung cancer staging. Furthermore, the echobronchoscope can also be inserted into the oesophagus, allowing sampling of lymph nodes not in contact with airways (*e.g.* stations 8 and 9), lung lesions adjacent to the oesophagus and left adrenal gland metastases.

Further reading

- Herth FJF, *et al.* (2006). Transbronchial and transesophageal (ultrasound guided) needle aspiration for the analysis of mediastinal lesions. *Eur Respir J*; 28: 1264–1275.
- Gasparini S (2010). Diagnostic management of solitary pulmonary nodule. *In:* Strausz J, *et al.*, eds. Interventional Pulmonology (ERS Monograph). Sheffield, European Respiratory Society; pp. 90–108.
- Gasparini S (2013). Conventional biopsy techniques. *In*: Ernst A, *et al.*, eds. Principles and practice of Interventional Pulmonology. New York, Springer; pp. 151–163.
- Gasparini S, *et al.* (1995). Integration of transbronchial and percutaneous approach in the diagnosis of peripheral pulmonary nodules or masses. *Chest*; 108: 131–137.
- Mazzone P, *et al.* (2002). Bronchoscopy and needle biopsy techniques for diagnosis and staging of lung cancer. *Clin Chest Med*; 23: 137–158.
- Shaham D (2000). Percutaneous transthoracic needle biopsy. *Radiol Clin North Am*; 38: 525–534.

Inhaled drug therapy

Omar S. Usmani

Inhaled drug therapy is the foundation of treatment in patients with respiratory disease and has several advantages over systemic drug therapy. By delivering the drug directly to the site of disease, inhaled therapy can minimise the side-effects that patients would otherwise experience from oral, intramuscular or intravenous treatment. A lower drug dose is required to achieve clinical benefit and the onset of action is quicker with the inhaled route.

Types of inhaler device

There are four classes of inhaler device: pressurised metered-dose inhaler (pMDI), dry powder inhaler (DPI), soft-mist inhaler (SMI) and nebuliser (table 1).

Pressurised metered-dose inhalers

pMDIs are the most commonly prescribed inhaler device in the world and contain a pressurised suspension of micronised drug particles in hydrofluorocarbon (HFC) propellant. pMDIs containing chlorofluorocarbon (CFC) propellant are now obsolete. pMDIs are compact, portable, low cost and have a wide variety of medications available. It is important to know that pMDIs can be divided into solution or suspension formulation devices. In suspension devices, the drug is soluble in the propellant requiring the device to be shaken before use to ensure a constant emitted drug dose at each actuation.

Following gentle exhalation to residual volume and shaking the device, pMDIs require patients to inhale slowly and gently, comfortably and deeply from the

Key points

- Improper inhaler training given to patients can lead to inhaler misuse, inhaler errors, lack of perceived clinical benefit and consequently nonadherence with the prescribed treatment.
- Patients may experience disease worsening or hospitalisations related primarily to their inability to engage with the device rather than pharmacological ineffectiveness.
- Choosing the right inhaler device for the patient is a critical part in our everyday management of patients with respiratory disease and is as important as tailoring the pharmacology to our patients.
- Inhalers are an integral part of the drug and the ‘inhaler opportunity’ to review inhaler technique should be addressed with each patient at every clinic visit.

Table 1. Main characteristics of available inhaler devices

Inhaler device	Advantages	Disadvantages
pMDI	Compact Familiarity to patient Low cost Metered dose Multidose Not dependent on patient inhalation flow Portable Wide variety of drugs	Cold freon effect Contain propellants that are greenhouse gases Coordination required Fast plume speed No dose counter Need to be shaken
pMDI with spacer	Can improve lung deposition Holds aerosol for short period prior to inhalation No coordination necessary Reduces deposition in mouth and pharynx Slows down aerosol plume	Bulky to carry around Requires regular cleaning Has propellant Some dose lost in spacer Static charge may be a problem
BA-pMDI	Compact Low inspiratory flow to trigger dose delivery No coordination required Portable	Cold freon effect Contain propellants that are greenhouse gases Fast plume speed No dose counter Need to be shaken
DPI	Compact Does not require propellants Multiple dose devices available No coordination required Portable	May be difficult to load Minimum inspiratory threshold by patient needed to generate dose Moisture sensitive Multiple designs (may be confusing to patients) Single capsule devices require loading each time
SMI	Auto-lock when cartridge is empty High fine particle fraction aerosol droplets Multidose No coordination required No spacer required Portable Slow aerosol mist velocity generated over 1.5 s	Only one device currently available Loading cartridge into device requires dexterity

(*Continued*)

Table 1. Continued

Inhaler device	Advantages	Disadvantages
Nebuliser	Deliver high doses of drug Dispense drugs not available as pMDI or DPI Tidal breathing Intelligent nebulisers allow more efficient delivery	Bulky Jet and ultrasonic nebulisers require external energy source Long treatment times Newer devices are expensive Older designs are very inefficient at delivery

device over 4–5 s; not fast and hard, as is often seen in daily practice. With respect to coordination of actuation with inhalation, a pragmatic approach is to ask the patient to actuate on the 'upstroke' in the first second of the inhalation phase. Often instructions are given to patients that actuation must be 'perfectly timed' with initiation of inhalation and patients become fearful of their inability to achieve this resulting to an improper inhalation. Where coordination is felt to be a concern, the use of a pMDI with a spacer may be helpful, especially in elderly patients with poor dexterity or in children. However, there is less of a need for spacers with pMDI devices that have a slower plume, long aerosol velocity, smaller drug particle size or high fine particle fraction as they achieve effective lung deposition independent from the patient's inhalation flow.

Another type of pMDI is the breath-actuated (BA)-pMDI, which may also be helpful in patients with poor coordination of actuation and inhalation as BA-pMDIs release the drug when the patient inhales and triggers the aerosol. The key point with all pMDIs is that the patient inhalation manoeuvre is the same; that is, slowly and deeply, irrespective of the prescribed brand of drug in the device mechanism, unlike DPI devices.

Dry powder inhalers

DPIs are portable devices that contain the dry powder drug as either a reservoir or capsule, usually with a carrier of lactose that keeps the formulation stable. These devices rely on the energy generated in the patient's respiratory muscles in order to generate effective airway inhalation flows in order to break up the dry powder and disperse it into the patient's airstream and achieve lung deposition. There are a huge variety of DPIs available to prescribe, and each brand has its own specific inhalation threshold to disperse the dry powder, unique dose preparation technique and particular handling instructions.

DPIs require patients to inhale forcefully, quickly and deeply and may require high inhalation flows (~60 L·min^{-1}). Even with an optimal patient inhalation technique, an incorrectly prepared dose from a DPI will be clinically ineffective. Some DPI devices are flow-dependent; that is, they vary in the dose delivered to the lungs in relation to the patient's inhalation flow through the device. Patients may also have suboptimal inspiratory flow from DPIs and this has been shown to lead to poor disease control and increase respiratory exacerbations in patients with asthma. In a similar manner to the development of the BA-pMDI, there are now DPIs that require low patient inhalation flows (~30 L·min^{-1}) to 'trigger' the dose from the aerosol device, and have advanced formulations with small particles that can achieve better levels of dose delivery to the lungs.

Soft-mist inhalers

The SMI is a unique class of inhaler device and there is only one type of device currently available. The SMI is a portable, nonpropellant inhaler device that uses the energy of a compressed spring to transform aqueous liquid solution inside the canister into an inhalable vapour. It does not require high patient inspiratory effort like DPIs. Instead,

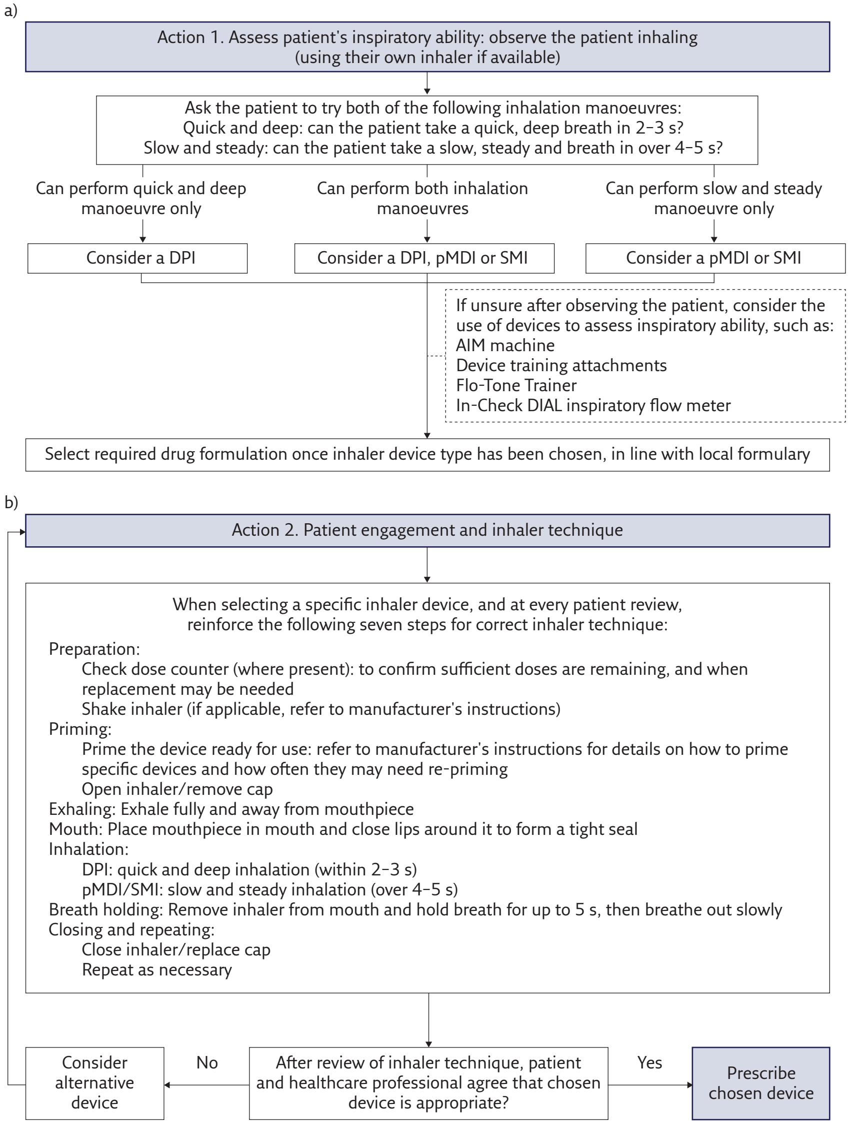

a)
Action 1. Assess patient's inspiratory ability: observe the patient inhaling (using their own inhaler if available)
Ask the patient to try both of the following inhalation manoeuvres:
Quick and deep: can the patient take a quick, deep breath in 2–3 s?
Slow and steady: can the patient take a slow, steady and breath in over 4–5 s?
Can perform quick and deep manoeuvre only
Can perform both inhalation manoeuvres
Can perform slow and steady manoeuvre only
Consider a DPI
Consider a DPI, pMDI or SMI
Consider a pMDI or SMI
If unsure after observing the patient, consider the use of devices to assess inspiratory ability, such as:
AIM machine
Device training attachments
Flo-Tone Trainer
In-Check DIAL inspiratory flow meter
Select required drug formulation once inhaler device type has been chosen, in line with local formulary
b)
Action 2. Patient engagement and inhaler technique
When selecting a specific inhaler device, and at every patient review, reinforce the following seven steps for correct inhaler technique:
Preparation:
Check dose counter (where present): to confirm sufficient doses are remaining, and when replacement may be needed
Shake inhaler (if applicable, refer to manufacturer's instructions)
Priming:
Prime the device ready for use: refer to manufacturer's instructions for details on how to prime specific devices and how often they may need re-priming
Open inhaler/remove cap
Exhaling: Exhale fully and away from mouthpiece
Mouth: Place mouthpiece in mouth and close lips around it to form a tight seal
Inhalation:
DPI: quick and deep inhalation (within 2–3 s)
pMDI/SMI: slow and steady inhalation (over 4–5 s)
Breath holding: Remove inhaler from mouth and hold breath for up to 5 s, then breathe out slowly
Closing and repeating:
Close inhaler/replace cap
Repeat as necessary
Consider alternative device
No
After review of inhaler technique, patient and healthcare professional agree that chosen device is appropriate?
Yes
Prescribe chosen device

Figure 1. Choosing an appropriate inhaler device. a) Assessment of the patient's inspiratory ability. b) Patient engagement and inhaler technique. Adapted from Usmani, et al. *Choosing an appropriate inhaler device for the treatment of adults with asthma or COPD.* In: *Hayeem N, ed. Guidelines—summarising clinical guidelines for primary care. 66th Edn. Chesham, MGP Ltd, 2018; pp. 279–281. Available at: www.guidelines.co.uk/respiratory/inhaler-choice-guideline. Reproduced with permission.*

the SMI requires a slow gentle and comfortable inhalation like pMDIs. The aerosol itself has a slow plume and velocity reducing impaction in the oropharynx and achieving good lung deposition of the delivered drug. The SMI requires dose preparation with the cartridge pushed into the canister that some elderly patients with poor dexterity may find difficult.

Nebulisers

Nebulisers are large, motor-driven inhaler devices and traditionally have been divided into jet nebulisers and ultrasonic nebulisers that continuously generate an aerosol. Vibration mesh nebulisers and adaptive aerosol delivery systems are newer nebulisers that pulse the drug only during the inhalation leading to little drug loss during the exhalation phase. Nebulisers are mainly used in emergency situations in order to deliver a high dose of drug to the lungs, or in patients with severe respiratory disease in hospital or at home who are unable to complete a proper inhalation manoeuvre for a DPI or MDI. Nebulisers are time-consuming and must be thoroughly cleaned to avoid microbial contamination

Choosing the right inhaler device

The training, teaching and use of inhaler devices by both patients and healthcare professionals alike can be challenging. Improper training given to patients can lead to inhaler misuse, inhaler errors, lack of perceived clinical benefit and consequently nonadherence with the prescribed treatment. Patients may experience disease worsening or hospitalisations related primarily to their inability to engage with the device rather than pharmacological ineffectiveness. Consequently, at review, healthcare professionals may inadvertently assume therapeutic ineffectiveness and increase the dose of the inhaled drug, compounding the situation without paying attention to the patients engagement with the inhaler device. A recent systematic review observed inhaler misuse led to worsening health outcomes and resources, emphasising the importance of achieving optimal inhaler technique.

Choosing the right inhaler device for the patient is a critical part in our everyday management of patients with respiratory disease and is as important as tailoring the pharmacology to our patients (figure 1). Inhalers are an integral part of the drug and the ‘inhaler opportunity’ to review inhaler technique should be addressed with each patient at every clinic visit.

Further reading

- Bonini M, *et al.* (2015). The importance of inhaler devices in the treatment of COPD. *COPD Research and Practice*; 1: 9.
- European Respiratory Society. Series on correct inhaler use. www.ers-education.org/e-learning/procedure-videos.aspx
- Lavorini F, *et al.* (2013). Correct inhalation technique is critical in achieving good asthma control. *Prim Care Respir J*; 22: 385–386.
- Lavorini F, *et al.* (2014). New inhaler devices – the good, the bad and the ugly. *Respiration*; 88: 3–15.
- Lavorini F, *et al.* (2017). Recent advances in capsule-based dry powder inhaler technology. *Multidiscip Respir Med*; 12: 11.
- Usmani OS, *et al.* (2018). Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. *Respir Res*; 19: 10.

Systemic pharmacotherapy

Mario Cazzola, Paola Rogliani and Maria Gabriella Matera

Need to also look beyond the lungs

Patients with COPD or asthma frequently suffer from concurrent comorbidities. COPD is strongly associated with cardiovascular disease (CVD), nonpsychotic mental disorders (including depressive disorders) and diabetes mellitus, but also with osteoporosis, malignant pulmonary neoplasms, skeletal muscle wasting and cachexia. Asthma is mainly associated with gastro-oesophageal reflux disease and allergic rhinitis, but also with obesity, depression, diabetes mellitus and CVD.

Many of these comorbidities have been related to low-grade systemic inflammation. The nature of this systemic inflammation remains unclear. It has been suggested that the most likely link between COPD and asthma and the extrapulmonary conditions is a simple spillover of inflammatory mediators from the pulmonary compartment, but this hypothesis is not proven. These systemic manifestations may actually result from shared genetic susceptibility, suggesting that therapies targeting these pathways have potential to treat several conditions simultaneously.

The presence of low-grade systemic inflammation clearly indicates that there is a strong need to look beyond the lungs in treating patients with COPD or asthma,

Key points

- Asthma and COPD are often associated with various comorbidities that may affect their clinical intensity and severity. While increasing evidence suggests that the systemic inflammatory pathway provides the common link between asthma or COPD and these comorbidities, the mechanisms by which the systemic component arises are unclear.
- The treatment of the comorbidities, mainly cardiovascular disease (CVD) or diabetes mellitus that occur simultaneously with chronic respiratory diseases, represents a fundamental need because it is likely that this approach can have a positive influence on the course of the respiratory disease.
- There is a clear need not only to control the underlying inflammatory processes of COPD or asthma, but also to reduce, as much as possible, systemic inflammatory state, which corresponds to adequately coping with the comorbidity.
- Potential links between asthma or COPD and CVD or type 2 diabetes mellitus have been identified, and pharmacological approaches that could be used to target these links have been suggested.

mainly when they also suffer from CVD or diabetes mellitus, because although low-grade systemic inflammation is not directly linked to organ damage, its presence is associated with an increased risk of developing some CVDs and metabolic diseases. Consequently, we must not only control the underlying inflammatory processes of COPD or asthma, but also reduce, as much as possible, systemic inflammatory state, which corresponds to adequately coping with the comorbidity. However, we still do not know whether the successful treatment of the comorbid diseases associated with COPD or asthma also positively influences the course of the lung disease.

Impact on the lung of cardiovascular drugs

Classes of drugs that are used for CVD, such as statins, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 (AT1) receptor blockers, and β-blockers may be useful in COPD and asthma.

Targeting the renin–angiotensin system

Angiotensin (Ang) II stimulates the release of cytokines including interleukin (IL)-6, tumour necrosis factor (TNF)-α and monocyte chemotactic protein-1, and has an immunomodulatory effect on T-cell responses. Furthermore, the AT1 receptor (AT_1R)/AT_2R ratio increases noticeably in regions of marked fibrosis surrounding bronchioles. These actions support a role for Ang II in inducing bronchoconstriction *via* the AT_1R. The renin–angiotensin system (RAS) can also generate reactive oxygen species *via* the AT_1R, promoting mitochondrial dysfunction, which contributes to the oxidative stress and impaired redox signalling observed in patients with COPD. ACE inhibitors and AT_1R antagonists also block the proinflammatory effect of Ang II.

ACE inhibitors and AT_1R blockers play a protective role against inflammation, vasoconstriction and small airway fibrosis induced by activation of RAS. In fact, there is evidence that the use of an ACE inhibitor is associated with preserved locomotor muscle mass, strength and walking speed, and that of AT_1R blockers seems to be associated with lower mortality, at least in COPD (figure 1).

Nevertheless, inhibition of the upstream Ang I/Ang II/AT_1R pathway by repositioning current renin inhibitors, ACE inhibitors or AT_1R blockers may dysregulate the degradation of bradykinin. In asthmatic airways, bradykinin provokes inflammatory oedema, mucus production, cough and smooth muscle contraction (cardinal signs of acute asthma) through the direct activation of bradykinin B_2 receptor, the neural cholinergic pathway and capsaicin-sensitive type C sensory nerve fibres (an effect referred to as ‘neurogenic inflammation’), and the release of various inflammatory mediators acting on endothelial, epithelial and smooth muscle cells. Consequently, since ACE inhibitors or AT_1R blockers may induce bronchoconstriction and dry cough, they should be prescribed with caution, especially for patients with severe asthma. Furthermore, some studies show an increased risk of anaphylaxis in patients who are taking ACE inhibitors. In fact, the activation of RAS, which is a compensatory mechanism caused by decreased peripheral vascular resistance, is blocked by ACE inhibitors, thus theoretically leading to intensified anaphylaxis.

Recent studies favour the development of compounds stimulating the ACE2/Ang (1–7)/Mas receptor pathway that serves to counter-regulate the proinflammatory, proproliferative and profibrotic effects of the ACE/Ang II/AT_1R pathway. This can be achieved by upregulating the activity of ACE2, the counteracting enzyme of ACE, with an ACE2 activator, direct supplementation with recombinant ACE2 or Mas receptor activation by Ang (1–7) peptide. It is likely that a combination of inhibitor of the Ang I/Ang II/AT_1R pathway and activator of the ACE2/Ang (1–7)/Mas receptor pathway may achieve optimal therapeutic effects for pulmonary diseases.

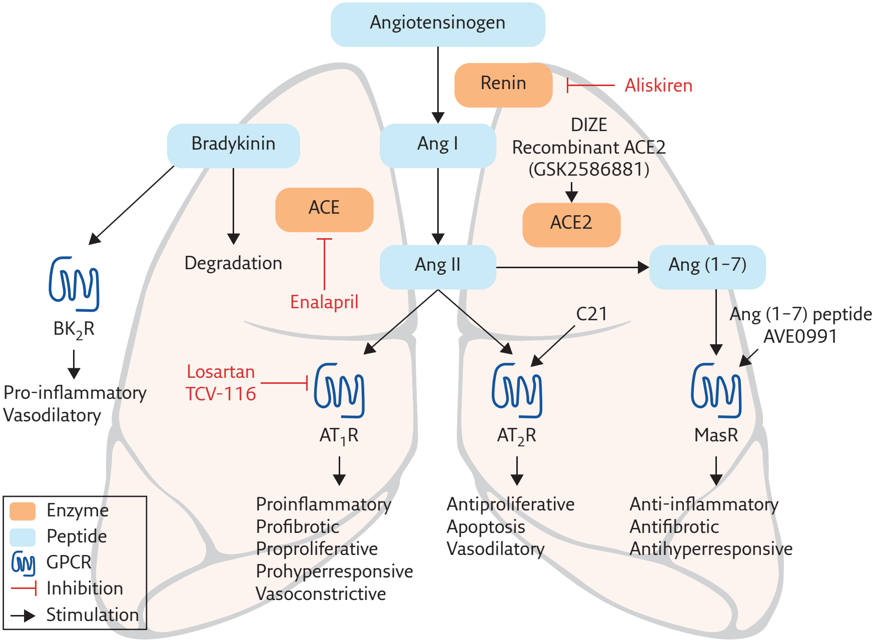

Angiotensinogen
Renin
Aliskiren
Bradykinin
Ang I
DIZE
Recombinant ACE2
(GSK2586881)
ACE
ACE2
Degradation
Ang II
Ang (1–7)
BK$_2$R
Enalapril
C21
Ang (1–7) peptide
AVE0991
Pro-inflammatory
Vasodilatory
Losartan
TCV-116
AT$_1$R
AT$_2$R
MasR
Enzyme
Peptide
GPCR
Inhibition
Stimulation
Proinflammatory
Profibrotic
Proproliferative
Prohyperresponsive
Vasoconstrictive
Antiproliferative
Apoptosis
Vasodilatory
Anti-inflammatory
Antifibrotic
Antihyperresponsive

Figure 1. The RAS and potential therapeutic targets for pulmonary diseases. DIZE: diminazene; BK$_2$R: bradykinin receptor; GPCR: G-protein coupled receptor. Reproduced and modified from Tan et al. *(2018) with permission from the publisher.*

Statins

Statins have several pharmacological actions that might be beneficial in the treatment of patients with COPD or asthma, including antioxidant, anti-inflammatory and immunomodulatory effects. The mechanism by which they could be used for the treatment of patients with COPD or asthma, involving the inhibition of the mevalonate pathway, seems to be the same as that observed for cholesterol lowering (figure 2). Inflammatory cells involved in lung and systemic inflammation, including eosinophils, neutrophils, macrophages, mast cells, T-cells and dendritic cells, are all affected by 3-hydroxy-3-methylglutaryl-coenzyme A reductase activity and mevalonate pathway metabolites and/or GTPases; this evidence collectively indicates a fundamental role for the mevalonate pathway in respiratory health and disease.

Nevertheless, in spite of the well-demonstrated pleiotropic effects of statins on airway inflammation and remodelling in both patients with COPD and asthma, and multiple observational studies showing efficacy of statins in reducing lung function decline and exacerbations, and improving symptom score and quality of life in these patients, randomised controlled trials have failed to show such benefit.

In any case, the documentation in a population-based cohort of patients with COPD that statin drug use may confer benefits regarding reduced lung-related and all-cause mortality, likely because it may reduce underlying systemic inflammation, which is often present in patients with COPD and is associated with increased mortality, indicates that it is appropriate to consider whether there is a specific COPD phenotype (patients with a high burden of systemic inflammation) that is more responsive to this treatment. Furthermore, preliminary findings suggest that statins may have clinical benefits and anti-inflammatory properties in smokers with asthma, and restore

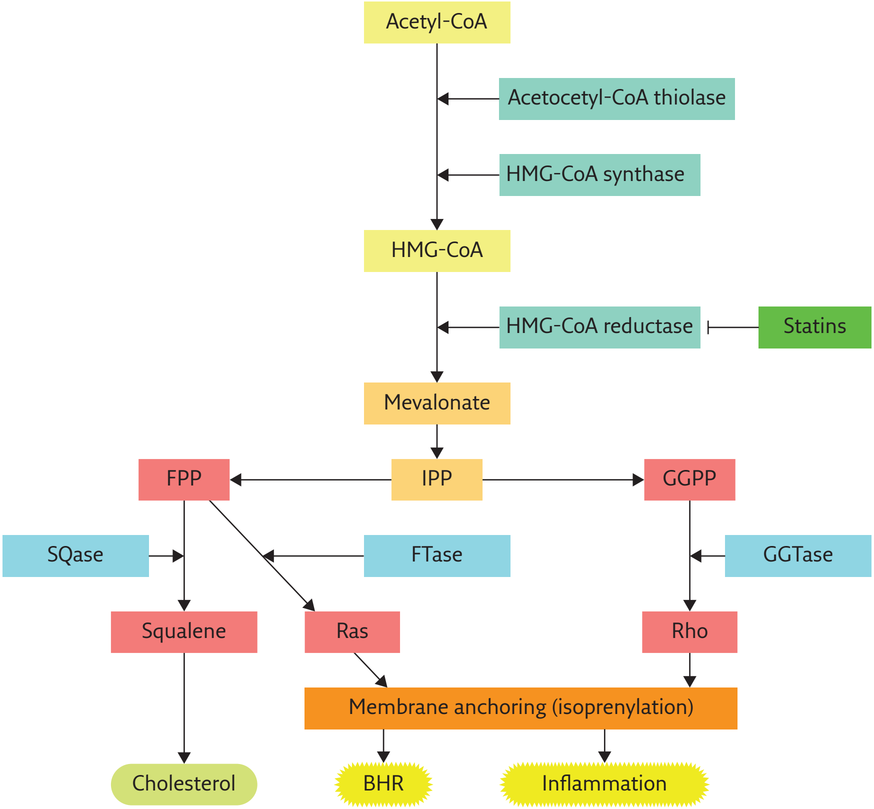

Acetyl-CoA
Acetocetyl-CoA thiolase
HMG-CoA synthase
HMG-CoA
HMG-CoA reductase
Statins
Mevalonate
FPP
IPP
GGPP
SQase
FTase
GGTase
Squalene
Ras
Rho
Membrane anchoring (isoprenylation)
Cholesterol
BHR
Inflammation

Figure 2. Mevalonate pathway and mechanism of action of statins. CoA: coenzyme A; HMG: 3-hydroxy-3-methylglutaryl; FPP: farnesylpyrophosphate; IPP: isopentenylpyrophosphate; GGPP: geranylgeranylpyrophosphate; SQase: squalene synthase; FTase: farnesyl protein transferase; GGTase: geranylgeranyl protein transferase; BHR: bronchial hyperresponsiveness. Reproduced from Cazzola et al. *(2017) with permission from the publisher.*

corticosteroid sensitivity in asthma and smoking-induced COPD. Nevertheless, further research is required.

β-blockers

In patients with pulmonary diseases, mainly those suffering from COPD, having concurrent ischaemic heart disease, hypertension and particularly heart failure, β-blockers seem to be an attractive option. Essentially, evidence from observational studies suggests that β-blockers are associated with various benefits in patients with COPD with or without CVD. β-blocker use in these patients may not only decrease the risk of overall mortality but also reduce that of exacerbations of COPD.

It has been suggested that reducing the sympathetic tone and upregulating β_2-adrenoceptors (β_2-ARs) in the lungs could be possible mechanisms by which β-blockers exhibit pulmonary beneficial effects in the long term in COPD (figure 3). In effect, an enhanced and sustained cardiac adrenergic drive occurs in patients with HF to aid in contraction, providing temporary relief to weakened heart muscles. In the long term, however, this stimulation causes cardiac myocytes to die. The activation of

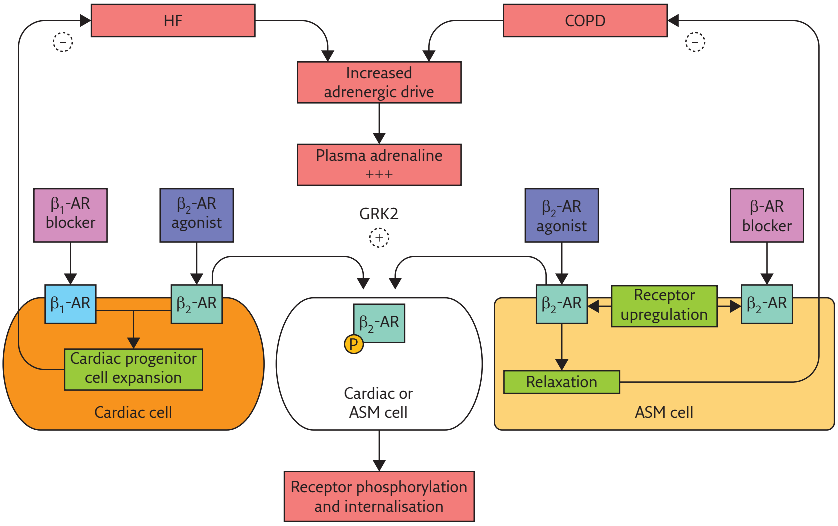

HF
COPD
Increased adrenergic drive
Plasma adrenaline +++
β_1-AR blocker
β_2-AR agonist
GRK2
+
β_2-AR agonist
β-AR blocker
–
–
β_1-AR
β_2-AR
Cardiac progenitor cell expansion
Cardiac cell
β_2-AR
P
Cardiac or ASM cell
β_2-AR
Receptor upregulation
β_2-AR
Relaxation
ASM cell
Receptor phosphorylation and internalisation

Figure 3. Pharmacological rationale for combining β-adrenoreceptor blockers and β_2-AR agonists in patients with COPD and concomitant heart failure. GRK2: G-protein coupled receptor kinase 2; ASM: airway smooth muscle. Reproduced from Cazzola et al. *(2017) with permission from the publisher.*

β_1-AR can induce myocardial cell hypertrophy, apoptosis, cell necrosis and myocardial remodelling activity in the earlier stage of HF.

The increased levels of plasma adrenaline also stimulate desensitisation of the β_2-ARs because of G-protein coupled receptor kinase 2 (GRK2)-mediated phosphorylation that leads to β_2-arrestin binding and receptor internalisation. These increased levels of plasma adrenaline result in a significant attenuation of relaxation of the airways, an effect that is reversed by treatment with a β-blocker that increases β_2-AR mRNA levels and decreases those of *GRK2* mRNA. This finding suggests that the long-term use of β-blockers can upregulate β_2-ARs in the lungs and thus, it reduces the need for β_2-agonists.

However, the co-administration of a β_2-agonist and a β_1-blocker can influence cardiac remodelling. β_2-AR signalling can grant protection against programmed cell death in myocytes, countering the proapoptotic action of β_1-AR stimulation *via* an inhibitory G-protein mediated process and promoting survival and proliferation responses. In fact, synergistic β_2-AR stimulation and β_1-AR blockade together may be efficacious for the expansion of cardiac progenitor cells in the failing heart.

Nevertheless, it must still be established whether a beneficial effect is achievable with all β-blockers or if only β-blockers that are β_2-AR inverse agonists, such as nadolol, must be prescribed. β_2-AR inverse agonists could inactivate the spontaneously active β_2-ARs and exert their beneficial effects on airway epithelial cells and immune cells by inhibiting constitutive proinflammatory signalling through noncanonical β_2-arrestin mediated signalling. Moreover, inactivation of β_2-ARs by inverse agonists inhibits phosphorylation of β_2-ARs, and thus desensitisation and downregulation.

In any case, the recommendations of the various clinical guidelines often disagree on the use of β-blockers in people with asthma, even those patients using β_1-AR selective drugs, because of the effects of dose-related β_2-AR blockade, which promotes cholinergic transmission and bronchoconstriction, especially upon first dose exposure. Nonetheless, if β_1-AR selective (cardioselective) β-blockers are indicated for acute cardiovascular events, asthma is not an absolute contraindication, but the relative risks/benefits should be considered. In fact, the adverse respiratory response from β-blockers in people with asthma and CVD varies according to β_1-AR selectivity, dose and duration of exposure. In contrast to oral nonselective β-blockers, oral β_1-AR selective β-blocker exposure is not associated with a significantly increased risk of asthma exacerbations and should potentially be considered more widely in people with strong clinical indications.

Impact on the lung of hypoglycaemic drugs

Potential links between asthma or COPD and type 2 diabetes mellitus (T2DM) have been identified and pharmacological approaches that could be used to target these links have been suggested. In particular, there is evidence that high glucose concentrations can lead to an enhanced responsiveness of human airway smooth muscle.

Sulfonylureas

It is now recognised that oral hypoglycaemic drugs also induce anti-inflammatory effects. There is evidence that the sulfonylurea glibenclamide is also a potent inhibitor of IL-1β activation in islets, whereas metformin inhibits the IL-1β-induced release of pro-inflammatory cytokines by inhibiting NF-κB (nuclear factor κ-light chain enhancer of activated B-cells) in macrophages and in the cells of the vascular wall. It has been shown that 2 months of daily metformin therapy in patients with T2DM inhibits the maturation of IL-1β in macrophages, an effect potentially relevant for the treatment of patients with COPD. Furthermore, studies on sulfonylureas provided evidence for safety in patients with diabetes combined with asthma by downregulation of allergic inflammation *via* IL-4/IL-13/ phosphorylated signal transducer and activator of transcription 6/vascular cell adhesion molecule-1 signalling pathway or by inhibiting cytokine-induced eosinophil survival and activation.

Glitazones

There is a special interest in thiazolidinediones (glitazones) that are selective agonists for the peroxisome proliferator-activated receptor (PPAR)-γ. This receptor is expressed in human monocytes and macrophages, which have also been shown to have potent anti-inflammatory effects in the lung. Glitazones downregulate NF-κB-mediated inflammatory pathways and reduce levels of TNF-α and IL-6. Several relevant pharmacological actions of PPAR-γ agonists have been demonstrated, such as effects on corticosteroid-resistant disease, tobacco smoke-induced pulmonary inflammation, skewing of macrophage phenotype and clearance of apoptotic neutrophils. The exposure to thiazolidinediones is associated with a small but significant reduction in risk for COPD exacerbation among patients with diabetes and concomitant COPD.

Glucagon-like polypeptide 1 receptor agonists

Incretins, such as glucagon-like polypeptide (GLP)1, are responsible for as much as half of the glucose-dependent insulin release after food ingestion and also suppress glucagon release. GLP1 regulates glucose homeostasis by binding to its specific receptor, GLP1-R. Patients with T2DM have reduced production and enhanced degradation of incretins by the enzyme dipeptidyl peptidase (DPP)-4. GLP1-Rs are present on human isolated bronchi. Furthermore, DPP-4 is amply expressed in the lung, where it activates proinflammatory pathways (mitogen-activated protein kinase and NF-κB), and may also increase the generation of reactive oxygen species and advanced glycation end-products (AGEs), and AGE receptor gene expression. Thus, upregulated DPP-4 may act to downregulate the benefits of GLP1. Exendin-4, which interacts with GLP1-R and has approximately 50–53% homology with human native GLP1, prevents the bronchial hyperresponsiveness mediated by glucose stimulation (figure 4). This protective action in the lung is mainly mediated by activating the cAMP/protein kinase A pathway, an effect analogous to that induced by β_2-agonists.

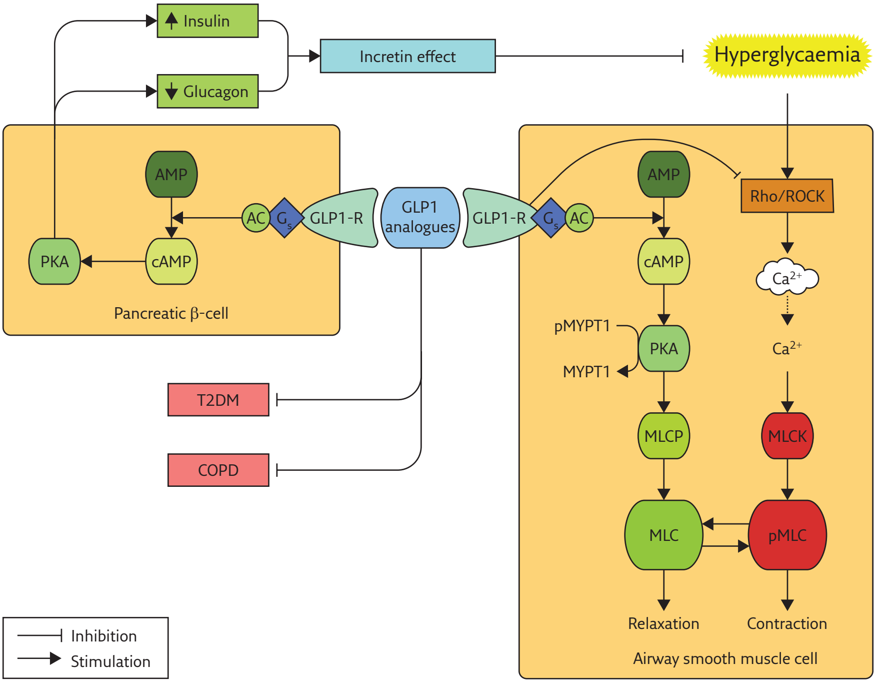

↑ Insulin
↓ Glucagon
Incretin effect
Hyperglycaemia
AMP
AC
G_s
GLP1-R
GLP1 analogues
GLP1-R
G_s
AC
AMP
Rho/ROCK
PKA
cAMP
cAMP
Ca^{2+}
Pancreatic β-cell
pMYPT1
PKA
Ca^{2+}
MYPT1
T2DM
MLCP
MLCK
COPD
MLC
pMLC
Relaxation
Contraction
Airway smooth muscle cell
Inhibition
Stimulation

Figure 4. Impact of GLP1 analogues on COPD and T2DM. GLP1 is an incretin hormone that increases glucose-stimulated insulin secretion and reduces glucagon release, and these effects are mediated by binding to its specific receptor (GLP1-R). GLP1 analogues stimulate glucose-dependent insulin release and inhibit glucagon secretion by activation of GLP1-Rs. Glucose can directly affect pulmonary bronchial tone and airway smooth muscle through the regulation of different molecular pathways in smooth muscle cells. In particular, increased activation of the Rho/ROCK pathway, together with the mobilisation of intracellular calcium and phosphorylation of myosin phosphatase target subunit (MYPT)1, is a molecular pathway affecting the pulmonary physiology associated with COPD in patients with T2DM; thus, modulation of these substrates could represent a novel therapeutic target for the treatment of COPD. GLP1-Rs are abundant in the lung. GLP1 analogues can prevent the bronchial hyperresponsiveness mediated by glucose stimulation. This protective action in the lung is mainly mediated by activating the cAMP/protein kinase (PK)A pathway and by inhibition of the Rho/ROCK-mediated Ca^{2+} sensitisation component. AC: adenylyl cyclase; G_s: stimulatory G-protein; pMYPT1: phosphorylated MYPT1; MLCP: myosin light chain phosphatase; MLCK: myosin light chain kinase; MLC: myosin light chain; pMLC: phosphorylated MLC. Reproduced and modified from Cazzola et al. *(2017) with permission from the publisher.*

ROCK inhibitors

The Rho/ROCK (Rho-associated coiled coil containing protein kinase) signalling pathway may also provide novel targets for the treatment of patients with both COPD and T2DM because this pathway, together with the mobilisation of intracellular calcium and the subsequent phosphorylation of myosin phosphatase target subunit 1, could have a crucial role in the reduced lung function observed in patients with diabetes. Targeting the Rho/ROCK axis could inhibit both inflammation and ASM contraction. Selective and nonselective ROCK inhibitors, including fasudil (approved for treatment of cerebral vasospasm in Japan and China), ripasudil and netarsudil (currently approved for treatment of glaucoma in Japan and the USA, respectively), have been developed, and others (*e.g.* Y-27632, H-1152, Wf-536, Y-39983, AMA-0076, GSK-269962A, SB-772077-B, SAR-407899, RKI-1447 and KD-025) are in development, but their oral use might be limited by the occurrence of dose-limiting adverse effects. However, local delivery of this class of drug topically to lungs as a dry powder or through nebulisation is potentially of interest to improve the tolerability of this approach.

Further reading

- Cazzola M, *et al.* (2017). Management of chronic obstructive pulmonary disease in patients with cardiovascular diseases. *Drugs*; 77: 721–732.
- Cazzola M, *et al.* (2017). Targeting mechanisms linking COPD to type 2 diabetes mellitus. *Trends Pharmacol Sci*; 38: 940–951.
- Matera MG, *et al.* (2012). Treatment of COPD: moving beyond the lungs. *Curr Opin Pharmacol*; 12: 315–322.
- Matera MG, *et al.* (2013). β-Adrenoceptor modulation in chronic obstructive pulmonary disease: present and future perspectives. *Drugs*; 73: 1653–1663.
- Rogliani P, *et al.* (2018). Pleiotropic effects of hypoglycemic agents: implications in asthma and COPD. *Curr Opin Pharmacol*; 40: 34–38.
- So JY, *et al.* (2018). Statins in the treatment of COPD and asthma – where do we stand? *Curr Opin Pharmacol*; 40: 26–33.
- Tan WSD, *et al.* (2018). Targeting the renin–angiotensin system as novel therapeutic strategy for pulmonary diseases. *Curr Opin Pharmacol*; 40: 9–17.

Allergen-specific immunotherapy

Christian Taube

The prevalence of allergic diseases is increasing worldwide. Allergic disease can manifest in a variety of different organ systems. The most important of these are allergic rhinoconjunctivitis, allergic asthma, atopic dermatitis, acute anaphylaxis and food allergy. The mechanisms underlying allergic reactions have been described in detail. Initially, sensitisation to a harmless allergen occurs, which induces a T-cell-mediated response with induction of an allergen-specific immunoglobulin E (IgE) response. Re-exposure to the allergen then results in IgE-mediated crosslinking of high-affinity IgE receptors (FcεRI), primarily on mast cells. This activation triggers the release of a variety of different mediators from mast cells, leading to an immediate allergic response. In addition, a late-phase response can be observed several hours after allergen exposure. Allergic reactions can be seasonal and/or perennial depending on the nature of the trigger(s) and patterns of exposure. Symptoms may be persistent or intermittent and vary depending on the organ system involved in the allergic reaction. In general, allergic diseases are common chronic conditions that can be associated with considerable morbidity and reduced quality of life.

There are several different treatment options for patients with allergic disease. If possible, avoidance measures can be implemented. However, complete avoidance of many allergens is not possible in daily life. Pharmacological therapies provide relief from symptoms, but do not modify the underlying pathophysiological mechanisms. Pharmacotherapy, especially for allergic rhinoconjunctivitis and allergic asthma, includes oral and topical antihistamines, topical (intranasal or inhaled) corticosteroids and anti-leukotriene agents, either as monotherapy or in combination.

Allergen immunotherapy (AIT) (also known as specific immunotherapy and allergen desensitisation) is another potential treatment option. The clinical indication for AIT

Key points

- Allergen immunotherapy (AIT) is a treatment option for patients with hymenoptera venom allergy.
- AIT can be considered in patients with allergic rhinitis and moderate-to-severe symptoms despite regular treatment and/or avoidance strategies.
- Individual product-based evaluation of the evidence for efficacy is recommended before treatment with a specific AIT.
- Absolute contraindications to AIT include severe or uncontrolled asthma, active systemic autoimmune disorders and active malignant neoplasia.

is dependent on the underlying allergic disease. AIT was first described more than 100 years ago, but there has been further development in the way AIT is administered, particularly over recent decades. The concept behind AIT is repeated application of the causative allergen, with the goal of inducing immune tolerance. Tolerance is a change in the immune response to the specific allergen, where no inflammatory reaction occurs following allergen exposure. The aim is to achieve long-lasting effects that persist even after discontinuation of therapy. The first step after initiation of AIT is desensitisation of FcεRI-bearing mast cells and basophils. In addition, AIT induces regulatory T-cells. This peripheral T-cell tolerance is critical to achieving long-lasting effects. In addition, AIT affects serum immunoglobulin levels. Serum-specific IgE levels often show a transient increase after AIT and then gradually decrease over months or years of continued treatment. In addition, an increase in allergen-specific IgG4 levels can be observed, which often accompanies clinical improvement. However, the exact role and effect of IgG4 in mediating the effectiveness of AIT is not well understood.

Route of delivery

Subcutaneous injection immunotherapy (SCIT) was the main approach to AIT initially, but there are also a growing number of oral and sublingual immunotherapy (SLIT) options available. Other approaches, such as intralymphatic injections, have been investigated in clinical studies but are not used in routine clinical practice. The choice of administration route is dependent on several factors, including the availability and funding of different formulations, the indication for treatment (*e.g.* only subcutaneous therapy is available for insect venom allergies), patient characteristics, physician or patient preference, and geographic location. To date, there have been no adequately powered direct head-to-head comparisons between SLIT and SCIT.

Insect venom

Hymenoptera venom allergy is associated with a potentially life-threatening allergic reaction following a bee, wasp or ant sting. Symptoms can range from an extensive local reaction to severe systemic reactions. Patients who have already experienced a severe reaction after an insect sting are advised to carry an adrenaline autoinjector, H1 antihistamines and oral glucocorticosteroids for use in case of future adverse allergic reactions. The only treatment that can prevent further systemic reactions is AIT with the appropriate insect venom. In this setting, AIT has been associated with a reduction in the frequency and severity of systemic reactions to future stings and/or a clinically relevant improvement in disease-specific quality of life. At present, insect venom AIT is only available in a subcutaneous formulation (SCIT). In addition, protocols for insect venom AIT have different build-up and maintenance doses, varying from conventional (12 weeks) to 1-day (ultra-rush) during the build-up phase. The time taken to reach the maintenance dose is dependent on the build-up phase. Treatment duration is usually from 3 to 5 years; however, for some conditions, like systemic mastocytosis, it can be lifelong.

Allergic rhinoconjunctivitis

Allergic rhinoconjunctivitis is characterised by nasal obstruction, a watery nasal discharge, sneezing and itching. These symptoms are often accompanied by conjunctivitis, with itching, infection and tearing. The basis of therapy is allergen avoidance, oral and topic antihistamines, topical corticosteroids and anti-leukotrienes. Inadequately controlled allergic rhinoconjunctivitis, despite optimal medical treatment, continues to represent a therapeutic challenge in the majority of patients. AIT is an option in these patients.

Several different SCIT and SLIT approaches are available. Data from numerous studies have shown that treatment with both SCIT and SLIT improves symptoms and reduces the need for additional medication, with benefits persisting after discontinuation of therapy. Treatment with AIT for 3–5 years is usually recommended. To date, there have been no direct head-to-head comparisons between SLIT and SCIT. Available data show that both approaches are effective. It is important to note that available therapies vary widely in their formulation and allergen content. Therefore, results from one preparation cannot be extrapolated to others. Many characterised, standardised, stable AIT preparations are available for common allergens, as recommended by European Medicines Agency (EMA). For less common allergens, such as moulds, a lack of standardised extracts may limit the effectiveness of AIT. Furthermore, activity and effectiveness may vary between batches in non-standardised preparations. Therefore, before starting therapy it is important to assess whether the chosen product has demonstrated effectiveness in the required indication in clinical studies.

Many patients with allergic rhinoconjunctivitis are not monosensitised but instead show sensitisation to several allergens. In this situation it is important to determine the clinical significance of each sensitisation and its relative contribution to the symptoms experienced. Patients can then be classified as monoallergic (where one allergen is driving symptoms) or polysensitised/polyallergic (where multiple allergens are driving symptoms). In monoallergic patients, AIT with the causative allergen is effective. A single allergen preparation may also be adequate in polyallergic patients with sensitisation to biologically related allergens. In patients with sensitisation to nonhomologous allergens, treatment with two of the most important allergens can be used.

Asthma

For patients with allergic asthma the optimal time for AIT is unclear. For those with allergic rhinoconjunctivitis and comorbid asthma, treatment with AIT seems to improve asthma-specific outcomes such as symptom scores, rescue medication use and allergen-specific hyperreactivity. However, these findings are based on a meta-analysis of heterogeneous studies and there is little current evidence that the addition of AIT to inhaled therapy in patients with allergic asthma improves lung function or decreases the number of exacerbations. However, an increasing number of clinical studies are investigating the effect of AIT in this patient group. The current Global Initiative for Asthma (GINA) guidelines state that AIT may be an option in patients for whom allergies play a prominent role. AIT, and especially SLIT, can be considered for adult patients with allergic rhinitis and sensitisation to house dust mite with exacerbations despite low- to high-dose inhaled corticosteroids. Current evidence suggests that SLIT can be used if the FEV_1 is >70% of predicted.

Side-effects

AIT is generally a safe and well-tolerated treatment. Systemic side-effects can occur, especially when using SCIT. Therefore, it is recommended that injections are given in a medical setting by trained staff, with immediate access to resuscitation equipment and a doctor trained in managing anaphylaxis. In addition, patients should remain under observation for at least 30 min after a SCIT injection.

The overall rate of any adverse reactions is similar for SCIT and SLIT, but severe systemic reactions appear to be much less likely with SLIT than SCIT. Severe reactions occur within 30 min of sublingual administration of allergens in droplet or tablet form. As a result, patients should be observed for at least 30 min after the first dose.

The majority of adverse events during SLIT develop at home. The most common effects are mucosal reactions (oral pruritus, swelling and throat irritation) or abdominal pain. The majority of these are self-limiting and occur during the first 3 weeks of therapy. Patients should stop therapy for a week in the presence of oral mucosal damage (*e.g.* after dental extraction or oral surgery).

Contraindications

There are some settings where the risk of AIT outweighs the expected benefits. Absolute contraindications for the initiation of AIT are uncontrolled or severe asthma, active systemic autoimmune disorders and active malignant neoplasia. In addition, AIT should not be initiated during pregnancy. If already underway, AIT may be continued during pregnancy or breastfeeding if previous doses have been well tolerated. Relative contraindications to AIT are a history of severe systemic reactions, beta-blocker therapy, severe cardiovascular disease, severe psychiatric disease and immunodeficiency. Initiation of AIT therapy that could continue for several years should be considered carefully in patients who have shown previous poor adherence to medical therapy.

Conclusion

AIT is an established treatment option for patients with hymenoptera venom allergy as well as for patients with allergic rhinitis. Different forms of application, like SCIT and SLIT, exist. To date, there have been no direct head-to-head comparisons between these two approaches. For asthma there is now increasing evidence for an efficacy of AIT, although additional studies are needed to clearly place this therapy in the therapeutic recommendations for patients with asthma.

Further reading

- Dhami S, *et al*. (2017). Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis. *Allergy*; 72: 1597–1631.
- Roberts G, *et al*. (2018). EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. *Allergy*; 73: 765–798.
- Sturm GJ, *et al*. (2018). EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy. *Allergy*; 73: 744–764.

Immunotherapies in lung cancer

Niels Reinmuth

Checkpoint inhibitors

Immune evasion is recognised as a key strategy for cancer survival and progression. Hence, a broad variety of therapeutic strategies have been developed, with the goal of promoting a host antitumour response. Since the immune response to an antigen is regulated by a balance between co-stimulatory and inhibitory signals (*e.g.* immune checkpoints), agents targeting immune checkpoints have gained considerable interest.

PD-1 signalling pathway

In various clinical trials, antibodies targeting the programmed cell death protein 1 (PD-1) or its ligand (PD-L1) have shown great potential for improving tumour responses and survival in lung cancer patients. So far, the European Medicines Agency (EMA) has currently approved the PD-1-targeting antibodies nivolumab and pembrolizumab and the PD-L1 antibody atezolizumab for treatment of advanced nonsmall cell lung cancer (NSCLC) in defined situations. It is expected that further anti-PD-1 and PD-L1 inhibitors will be approved in the near future.

CTLA4 blockade

Besides the PD-1 axis, strategies blocking the activation of the cytotoxic T-lymphocyte-associated antigen 4 (CTLA4; also known as CD152) pathway have been studied. However, phase III trials have failed to demonstrate a significant survival benefit from

Key points

- PD-1 and PD-L1 checkpoint inhibitors have demonstrated clinical activity in stage IV nonsmall cell lung cancer (NSCLC).
- Checkpoint inhibitors in combination with chemotherapy are expected to be a standard therapy in untreated stage IV NSCLC.
- Additive anti-PD-L1 therapy following chemoradiotherapy in stage III NSCLC leads to extended progression-free survival.
- Safety of checkpoint inhibitors is manageable, but a broad variety of side-effects can occur.
- As a predictive marker for likelihood of clinical efficacy, PD-L1 expression has emerged. Additional markers such as tumour mutational burden are being developed.

adding the CTLA4 antibody ipilimumab to platinum-based chemotherapy in NSCLC or small cell lung cancer (SCLC) patients. Currently, CTLA4 antibodies such as ipilimumab or tremelimumab are being evaluated in various combinations, as for PD-1 or PD-L1 antibodies.

Pretreated locally advanced or metastatic NSCLC

Several studies have demonstrated a significant overall survival benefit for various PD-1 or PD-L1 antibodies as monotherapy *versus* docetaxel (table 1). Consequently, these agents have been adopted in unselected (nivolumab and atezolizumab) or PD-L1-expressing (pembrolizumab) NSCLC tumours as a standard of care after progression on first-line cytotoxic therapy. Side-effects were comparable between studies, all indicating that checkpoint inhibitors have a characteristic side-effect profile that is distinct from that of cytotoxic therapy. The most relevant side-effects reported are fatigue, rash, liver enzyme elevation, colitis, hormone depletion and pneumonitis. However, most immune-related adverse events tend to be of low grade, reversible and inflammatory in nature. Recently, recommendations regarding the management of immune-related adverse events have been published by the European Society for Medical Oncology. Collectively, the tolerability of monotherapy of PD-1 or PD-L1 inhibitors has been evaluated as superior to that of docetaxel.

Untreated stage IV NSCLC

In the first-line NSCLC setting, pembrolizumab was established as a new standard of care for patients with metastatic NSCLC with tumour PD-L1 expression levels of at least 50%, leading to an overall survival improvement compared to platinum-based cytotoxic therapy (hazard ratio for death of 0.60; Reck *et al*., 2016a).

Cytotoxic therapy could synergise with immunotherapy by various mechanisms, including killing tumour cells, releasing antigens and reducing immunosuppressive

Table 1. Checkpoint inhibitors versus *docetaxel in selected phase III studies*

Compound	Phase III trial	ORR	PFS months	OS months	Reference
Nivolumab	Checkmate 017	20%	3.5 (2.1–4.9)	9.2 (7.3–13.3)	Brahmer *et al*. (2015)
	Checkmate 057	19.2%	2.3 (2.2–3.3)	12.2 (9.7–15.0)	Borghaei *et al*. (2015)
Pembrolizumab	Keynote 010 (PD-L1 TPS ≥1%)	18%			Herbst *et al*. (2015)
	2 mg·kg^{-1}		3.9 (3.1–4.1)	10.4 (9.4–11.9)	
	10 mg·kg^{-1}		4.0 (2.7–4.3)	12.7 (10.0–17.3)	
Atezolizumab	OAK	14%	2.8 (2.6–3.0)	13.8 (11.8–15.7)	Rittmeyer *et al*. (2017)

Data are presented as survival rate (95% CI), unless otherwise stated. ORR: overall response rate; PFS: progression-free survival; OS: overall survival; TPS: tumour proportion score.

factors. Very recently, several phase III trials have indicated that the combination of checkpoint inhibitors with platinum-based chemotherapy can lead to improved progression-free and overall survival, at least in broad subgroups of patients (table 2). However, since most data reported so far are derived from interim analyses, follow-up reports are warranted. Side-effects were somewhat higher compared to chemotherapy alone but were seen as tolerable in general, at least for the patients with good performance status that were included in these studies.

Of note, a chemotherapy-lacking combination of nivolumab with ipilimumab led to a significantly improved progression-free survival compared to platinum-based chemotherapy, which was restricted to patients with high tumour mutational burden (Hellmann *et al*., 2018). However, overall survival has not been reported yet. Also, the safety profile for such combinations does not seem to be as clinically favourable as those with PD-1/PD-L1 inhibitors plus cytotoxic therapy combinations, especially in terms of immune-related adverse events.

Table 2. Checkpoint inhibitors as monotherapy or in combination with chemotherapy in selected phase III studies

Selection	Comparison	ORR	Hazard ratios		Reference
			PFS	OS	
PD-L1 ≥50%	Pembrolizumab *versus* platinum-based chemotherapy	44.8% *versus* 27.8%	0.50 (p<0.01)	0.60 (p<0.01)	Reck *et al*. (2016a)
PD-L1 ≥1%	Pembrolizumab *versus* platinum-based chemotherapy	27.3% *versus* 26.5%	1.07 (NS)	0.81 (p<0.01)	Lopes *et al*. (2018)
Nonsquamous NSCLC	Carboplatin plus pemetrexed ± pembrolizumab	47.6% *versus* 18.9%	0.52 (p<0.01)	0.49 (p<0.01)	Gandhi *et al*. (2018)
Squamous NSCLC	Carboplatin plus (paclitaxel or nab-paclitaxel) ± pembrolizumab	58% *versus* 35%	0.56 (p<0.01)	0.64 (p<0.01)	Paz-Ares *et al*. (2018)
Squamous NSCLC	Carboplatin plus nab-paclitaxel ± atezolizumab (study arm B *versus* C)	59.4% *versus* 51.3%	0.715 (p<0.01)	0.96 (NS)	Jotte *et al*. (2018)
Nonsquamous NSCLC	Carboplatin, paclitaxel, bevacizumab ± atezolizumab	64% *versus* 48%	0.59 (p<0.01)	0.78 (p=0.0164)	Socinski *et al*. (2018)
TMB ≥10 mutations per megabase	Nivolumab/ ipilimumab *versus* platinum-doublet	45.3% *versus* 26.9%	0.58 (p<0.01)	Immature	Hellmann *et al*. (2018)

ORR: overall response rate; PFS: progression-free survival; OS: overall survival; TMB: tumour mutational burden; NS: nonsignificant.

Nonmetastatic NSCLC

In patients with locally advanced, unresectable NSCLC, a phase III study demonstrated a significantly prolonged progression-free survival with durvalumab *versus* placebo as consolidation therapy after chemoradiotherapy including at least two cycles of platinum-based chemotherapy (hazard ratio for disease progression or death of 0.52, $p<0.001$; Antonia *et al*., 2017). Consequently, the median time to death or distant metastasis was longer with durvalumab than placebo (23.2 *versus* 14.6 months, $p<0.001$). Interestingly, safety was similar between the groups, indicating an only slightly increased grade 3 or 4 pneumonia rate (4.4% and 3.8% for durvalumab and placebo, respectively). Overall survival has not been reported yet. While durvalumab has been approved by the US Food and Drug Administration (FDA) in this setting, a decision by the EMA is pending.

In another study, two cycles of neoadjuvant nivolumab in patients with surgically resectable early-stage NSCLC led to a major pathological response in 45% of the resected tumours (Forde *et al*., 2018). Interestingly, responses occurred in both PD-L1-positive and PD-L1-negative tumours. Again, a significant correlation between the pathological response and the tumour mutational burden was noted.

Predictive markers

In all studies, a correlation between PD-L1 expression and clinical activity of PD-1 or PD-L1 inhibitors was noted. For all PD-1/PD-L1 antibodies, different companion immunohistochemistry tests have been developed for detecting PD-L1 expression in tumour cells, immune cells or both. However, even in tumours lacking a PD-L1 expression, a subset of patients benefits from these agents. Tumour mutational burden as a surrogate marker of neo-antigen load has been identified as another promising marker that might harbour predictive value independently of PD-L1 expression. However, only limited data have been generated so far and the cut-off correlates to the analytical test applied. In a recent phase III study by Hellmann *et al*. (2018), the cut-off for identifying patients with high tumour mutational burden was set at 10 mutations per megabase using a commercially available next-generation sequencing assay analysing 324 genes. Collectively, both tumour mutational burden and PD-L1 expression may predict benefit from immune checkpoint inhibitors. In addition, further predictive markers such as CD8 density and interferon-γ signatures are in clinical development.

Ongoing studies

A plethora of clinical studies is currently ongoing. In particular, checkpoint inhibitors are being explored as monotherapy in NSCLC and SCLC patients as well as in combination with cytotoxic agents, radiotherapy and other checkpoint inhibitors. Moreover, further PD-1 and PD-L1 inhibitors such as avelumab and durvalumab are being evaluated. Also, several other agents that target other signalling pathways within the immune checkpoint system are currently in development, including IDO1, KIR and LAG-3. These agents are being investigated either alone or in combination with other immune checkpoint inhibitors. Moreover, co-stimulatory molecules such as OX40, which act in the opposite way to inhibitory checkpoints, represent another type of promising target with immune modulatory function.

Further reading

- Antonia SJ, *et al.* (2017). Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*; 377: 1919–1929.
- Borghaei H, *et al.* (2015). Nivolumab *versus* docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*; 373: 1627–1639.
- Brahmer J, *et al.* (2015). Nivolumab *versus* docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*; 373: 123–135.
- Forde PM, *et al.* (2018). Neoadjuvant PD-1 blockade in resectable lung cancer. *N Engl J Med*; 378: 1976–1986.
- Gandhi L, *et al.* (2018). Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*; 378: 2078–2092.
- Govindan R, *et al.* (2017). Phase III trial of ipilimumab combined with paclitaxel and carboplatin in advanced squamous non-small-cell lung cancer. *J Clin Oncol*; 35: 3449–3457.
- Haanen J, *et al.* (2017). Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*; 28: Suppl. 4, iv119–iv142.
- Hellmann MD, *et al.* (2018). Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med*; 378: 2093–2104.
- Herbst RS, *et al.* (2015). Pembrolizumab *versus* docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*; 387: 1540–1550.
- Herbst RS, *et al.* (2018). The biology and management of non-small cell lung cancer. *Nature*; 553: 446–454.
- Jotte RM, *et al.* (2018). IMpower131: Primary PFS and safety analysis of a randomized phase III study of atezolizumab+carboplatin+paclitaxel or nab-paclitaxel *vs* carboplatin+nab-paclitaxel as 1L therapy in advanced squamous NSCLC. *J Clin Oncol*; 36: Suppl. 18, LBA9000.
- Lopes G, *et al.* (2018). Pembrolizumab (pembro) *versus* platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥1%: open-label, phase 3 KEYNOTE-042 study. *J Clin Oncol*; 36: Suppl. 18, LBA4.
- Paz-Ares L, *et al.* (2018). Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*; 379: 2040–2051.
- Reck M, *et al.* (2016a). Pembrolizumab *versus* chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*; 375: 1823–1833.
- Reck M, *et al.* (2016b). Phase III randomized trial of ipilimumab plus etoposide and platinum *versus* placebo plus etoposide and platinum in extensive-stage small-cell lung cancer. *J Clin Oncol*; 34: 3740–3748.
- Reinmuth N, *et al.* (2016). Immunotherapy for lung cancer. *Oncol Res Treat*; 39: 360–368.
- Rittmeyer A, *et al.* (2017). Atezolizumab *versus* docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*; 389: 255–265.
- Socinski MA, *et al.* (2018). Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*; 378: 2288–2301.
- Swann JB, *et al.* (2007). Immune surveillance of tumors. *J Clin Invest*; 117: 1137–1146.

Respiratory physiotherapy

Thierry Troosters and Julia Bott

Respiratory physiotherapy should be offered to patients with a variety of medical respiratory conditions, with the aim of breathlessness management and symptom control, mobility and function improvement or maintenance, and airway clearance and cough enhancement or support (Bott *et al.*, 2009). Respiratory physiotherapy spans a broad range of services, advice and non-pharmacological interventions, and is used to help patients with a variety of respiratory conditions. The areas where respiratory physiotherapists have developed expertise were recently summarised in the European Respiratory Society's syllabus for respiratory physiotherapy. It was acknowledged that respiratory physiotherapists frequently subspecialise, with a focus either on chronic, acute or critical care, and either in adults or in children.

General principles of physiotherapy

Physiotherapy aims at treating or alleviating problems rather than diseases. Strategies are used to restore, improve or maintain movement and/or function, and maximise participation in everyday life using the framework of the World Health Organization's International Classification of Functioning, Disability and Health. Physiotherapists are thus vital to the delivery of effective pulmonary rehabilitation.

Physiotherapy is provided across all healthcare settings. Physiotherapists can work independently or as a member of a multidisciplinary team. Respiratory physiotherapists are well qualified to provide assessment and monitoring of, for example, ventilatory function and cough effectiveness or exercise tolerance,

Key points

Physiotherapy is indicated in most respiratory conditions for:

- Self-management advice and education on lifestyle modifications;
- Symptom management *e.g.* breathlessness, fatigue, anxiety, cough;
- Improvement or maintenance of mobility and function;
- Airway clearance in well-defined cases;
- Promoting physical activity, and prescription of exercise and exercise training;
- Prescription of walking aids;
- Improvement of respiratory mechanics; and
- Improvement of gas exchange *e.g.* V'_E/perfusion matching.

including for ambulatory oxygen assessment. Beyond the respiratory problems tackled, physiotherapy is commonly helpful for postural problems and/or musculoskeletal dysfunction and pain, as well as for improving continence. This is especially warranted during coughing and forced expiratory manoeuvres, where stress incontinence is particularly prevalent.

Airway clearance

To help the patient better manage their secretions, a range of airway clearance techniques (ACTs) are available, including:

- Independent techniques
- Mechanical or other devices
- Postural drainage
- Nebulised substances (*e.g.* hypertonic saline)
- Forced expiratory techniques and techniques for cough enhancement or support

The most effective techniques are those which include forced expiratory techniques, which make use of an increased airflow over mucus accumulating in the airways.

Physiotherapists are well placed to assist in the delivery of (inhaled) pharmacotherapy and their timing with respect to the airway clearance and physical activity physiotherapy interventions.

Strategies to enhance ventilation and gas exchange

Physiotherapists play an important role in the prevention and treatment of hypoventilation and improvement of gas exchange. This is helpful in stable patients (*e.g.* a patient with neuromuscular disease) as well as in acute patients (*e.g.* during exacerbations, after thoracic surgery or in the intensive care unit (ICU)). Evidence based strategies to enhance ventilation and gas exchange include:

- Positioning
- Breathing techniques
- Manual hyperinflation
- Intermittent positive pressure breathing (IPPB)
- CPAP
- NIV

These techniques are offered often in conjunction with other efforts from members of a multidisciplinary team, for example nurses or speech and language therapists.

Physiotherapists can also help in the delivery and correct application of oxygen therapy, including long-term and ambulatory oxygen, as well as in offering improvement of poor ventilatory function, including in the sedated and paralysed patient.

Disease-specific physiotherapy

Chronic obstructive pulmonary disease

Respiratory physiotherapy has been used for a long time in COPD and practice guidelines do exist (Langer *et al.*, 2009). Physiotherapy breathlessness management includes:

- Positioning to fix the shoulder girdle passively
- Forward-leaning postures to improve the length/tension ratio of the diaphragm

- Providing support with wheeled walking aids to assist further with either or both of the above points
- Breathing techniques help the patient better control dyspnoea and panic, both at rest and during exertion, for example using pursed lips breathing

Physical activity and exercise are of paramount importance throughout the course of the disease, including during hospital admission where possible and appropriate. When supervised and carried out at an appropriate intensity these exercises are more effective. Exercise training programmes are indicated for patients who have symptoms and impaired physical activities in daily life (see the chapter on Pulmonary rehabilitation). Selected patients may benefit from inspiratory muscle training to alleviate symptoms of dyspnoea and in some patients to help increase exercise tolerance. The use of wheeled walking aids, particularly in the most impaired patients, may be useful to reduce the ventilator requirements and enhance walking efficiency.

ACTs are only indicated when excess sputum is produced and patients are unable to spontaneously cough mucus up. There is no indication for mucus clearance physiotherapy in all patients with COPD. Even in acute exacerbations of COPD, there is no indication for systematic mucus clearance therapy when patients have a productive spontaneous cough. However, when patients experience retention of secretions, the assistance of a physiotherapist may be warranted to help with cough effectiveness, such as the use of forced expiratory techniques or positive expiratory pressure (PEP) devices (Tang *et al*., 2010). In patients who are too weak or tired to generate an effective cough, temporary assist can be provided with IPPB or longer-term by NIV.

Asthma

Some form of breathing retraining, to reduce respiratory rate, minute volume and to promote relaxed diaphragmatic breathing, can be helpful to reduce asthma symptoms and improve quality of life, along with prescribed medication (Bruton *et al*., 2018 and British Thoracic Society *et al*., 2016). It is important to stress that these techniques are adjunctive to medication and not a replacement therapy as they do not affect lung function or airways inflammation. Routine or regular airway clearance is rarely indicated in the asthmatic patient. Patients are also encouraged to take part in regular sports. When patients are deconditioned, specific rehabilitation programs are indicated (see the chapter on Pulmonary rehabilitation).

Dysfunctional breathing (hyperventilation syndrome)

Dysfunctional breathing is a term describing a group of breathing disorders in patients where chronic changes in breathing pattern result in dyspnoea and often non-respiratory symptoms in the absence of, or in excess of, organic respiratory disease (Boulding *et al*., 2016). Often this has a psychological basis (anxiety). It is severely disabling and can lead to emergency admission and excessive utilisation of healthcare resources. It often involves deep and/or rapid breathing which results in respiratory symptoms. Breathing exercises, with an emphasis on slow, nasal breathing and either a smaller tidal volume or lower respiratory rate, or both, to reduce V'_E, combined with relaxation (technique as for asthma), are often prescribed to reduce symptoms once the diagnosis is confirmed. While these techniques are often empirically used, and predominantly serve to gain a sense of 'breathing control', the solid evidence base is largely missing both in adults and in children.

CF and non-CF bronchiectasis

Physiotherapy is integral to the management of patients with bronchiectasis arising from any cause, including CF, with airway clearance and exercise training being central to this therapy. A recent European Respiratory Society (ERS) guideline (Polverino *et al.*, 2017) strongly recommended that patients suffering from bronchiectasis and impaired exercise tolerance should take part in a pulmonary rehabilitation programme (strong recommendation, high quality evidence). Evidence for ACTs was weaker, although airway clearance was still recommended for patients with chronic productive cough or difficult to expectorate sputum. More recently, compelling evidence showed that specific mucus clearance techniques, applied for a year, reduced exacerbation frequency and improved health-related quality of life (Muñoz *et al.*, 2018), further strengthening the evidence base for the ERS recommendation. Figure 1 offers an overview of the proposed interventions for the physiotherapy approach in bronchiectasis according to the ERS guideline. This could be applied for both CF and non-CF bronchiectasis.

A variety of airway clearance techniques, including those with and without mechanical assistance if necessary, can be offered to find one that is both acceptable and effective in an individual patient. The simplest technique that impinges the least on the patient's life is a good starting point.

Effective treatment might need to be supported by inhaled therapies (*e.g.* bronchodilators or hypertonic saline, oxygen and NIV or IPPB). These supportive therapies and postural drainage to enhance airway clearance or exercise training as part of the mucus clearance should be assessed for benefit on an individual basis. Regular review is advised to ensure continuing effectiveness and concordance with therapy; appropriate adjustment of treatment can be made if necessary. An Australian practice guideline on respiratory physiotherapy (Button *et al.*, 2016) summarised the evidence for airway clearance in CF as follows.

- ACTs should be applied across the lifespan in CF.
- The active cycle of breathing techniques can be used for airway clearance in people with acute or chronic lung disease independently or in conjunction with other airway clearance techniques.
- PEP, oscillating PEP and autogenic drainage are effective forms of airway clearance, which can be performed independently.
- Postural drainage with a head-down position should not be routinely used in infants with CF or in patients of any age with gastro-oesophageal reflux (GOR). Modified postural drainage is recommended in infants and young children where active participation in airway clearance is not possible.
- Physical exercise can be used to reduce the mechanical impedance of sputum, achieve short-term improvements in lung function and improve ease of expectoration.

Hygiene measures are crucially important in the management if CF and this includes measures taken during respiratory physiotherapy. Specific attention is required for any aids used in this therapy.

In addition to the respiratory problems, physiotherapists can address postural problems in these patient and problems of stress incontinence.

Interstitial lung diseases

There is little published evidence on physiotherapy for interstitial lung diseases (ILDs). Exercise training and pulmonary rehabilitation is effective in these patients, particularly when referred early in the disease process. With longer programmes, effects on exercise tolerance and health-related quality of life may persist (Perez-Bogerd *et al.*, 2018).

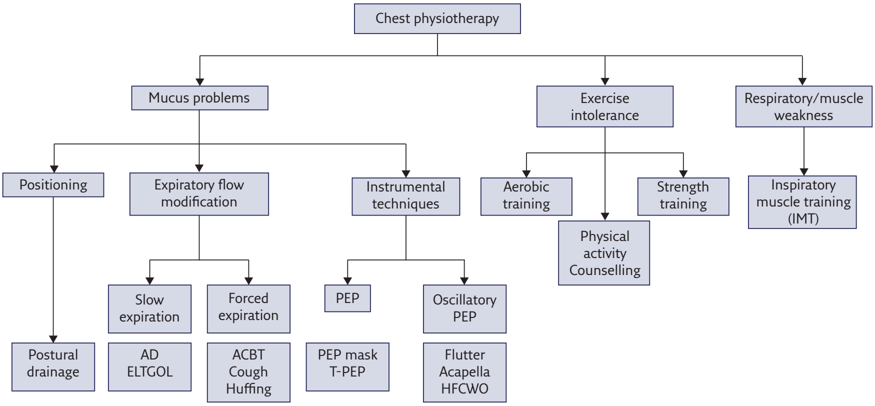

Chest physiotherapy
Mucus problems
Exercise intolerance
Respiratory/muscle weakness
Positioning
Expiratory flow modification
Instrumental techniques
Aerobic training
Strength training
Physical activity Counselling
Inspiratory muscle training (IMT)
Slow expiration
Forced expiration
PEP
Oscillatory PEP
Postural drainage
AD ELTGOL
ACBT Cough Huffing
PEP mask T-PEP
Flutter Acapella HFCWO

Figure 1. Chest physiotherapy interventions in bronchiectasis. AD: autogenic drainage; ELTGOL: total slow expiration with open glottis and infralateral position; ACBT: active cycle of breathing techniques; T-PEP: temporary positive expiratory pressure; HFCWO: high frequency chest wall oscillation. Reproduced from Polverino et al. *(2017).*

Patients at a later stage of disease may benefit from wheeled walking aids, ambulatory oxygen, breathlessness management and energy conservation strategies.

Community-acquired pneumonia

ACTs are rarely indicated.

For patients admitted to hospital with uncomplicated community-acquired pneumonia (CAP):

- Regular use of PEP may reduce length of stay
- Medical condition permitting, early mobilisation is indicated
- Patients should be encouraged to sit out of bed for ≥20 min on the first day, increasing the time and general mobility on each subsequent day

CPAP may be helpful for patients in type 1 respiratory failure who remain hypoxaemic despite optimum medical therapy and oxygen, and NIV may be an option for selected patients in type II respiratory failure, especially those with underlying COPD.

Chest wall disorders

Pulmonary rehabilitation is indicated in a patient with chest wall deformity from any cause with reduced exercise capacity and/or breathlessness on exertion. The need for ambulatory oxygen or NIV should be assessed before undertaking exercise. Respiratory muscle training may have a role when inspiratory muscle function is impaired. Whether breathing or thoracic mobility exercises are helpful in this patient group needs to be further proven.

Neuromuscular disease and spinal cord injury

Respiratory problems are the most common cause of morbidity and mortality for those with respiratory muscle weakness; physiotherapy therefore provides vital assistance with airway clearance by providing cough augmentation and sputum mobilisation (figure 2).

Difficulty clearing secretions may be due to inspiratory, expiratory and/or bulbar muscle weakness, depending on the underlying condition and stage of disease.

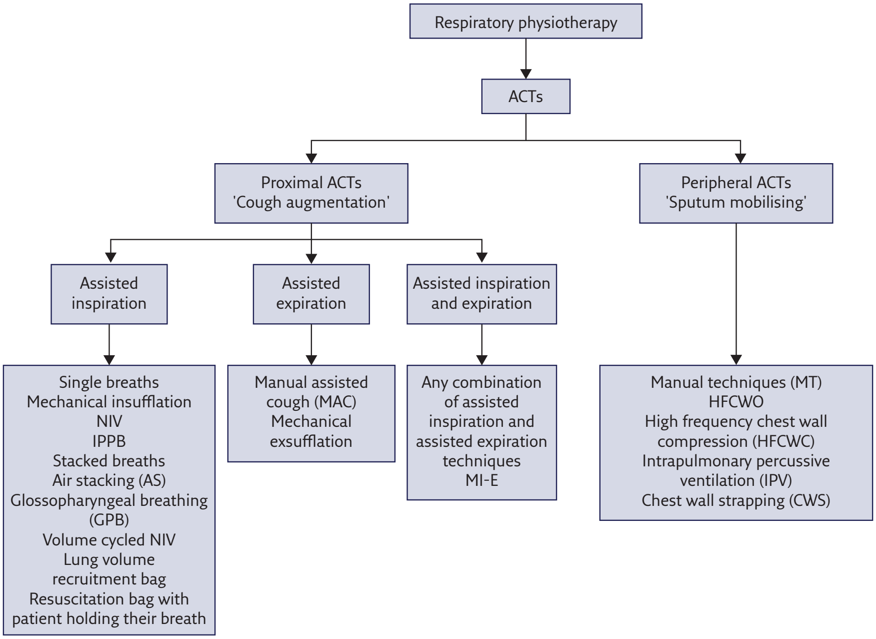

Respiratory physiotherapy
ACTs
Proximal ACTs 'Cough augmentation'
Peripheral ACTs 'Sputum mobilising'
Assisted inspiration
Assisted expiration
Assisted inspiration and expiration
Single breaths
Mechanical insufflation
NIV
IPPB
Stacked breaths
Air stacking (AS)
Glossopharyngeal breathing (GPB)
Volume cycled NIV
Lung volume recruitment bag
Resuscitation bag with patient holding their breath
Manual assisted cough (MAC)
Mechanical exsufflation
Any combination of assisted inspiration and assisted expiration techniques
MI-E
Manual techniques (MT)
HFCWO
High frequency chest wall compression (HFCWC)
Intrapulmonary percussive ventilation (IPV)
Chest wall strapping (CWS)

Figure 2. The classification of ACTs that are used in individuals with neuromuscular disease. Single breaths are defined as a breath given to the individual by the device followed by them exhaling or coughing. Stacked breaths are defined as multiple breaths in without the individual breathing out after the inspiration. Once the individual is close to their total inspiratory capacity they can actively or passively exhale, or cough. Mechanical insufflation is defined as an insufflation only provided by a positive pressure device. Mechanical exsufflation is defined as an exsufflation only provided by a mechanical insufflation–exsufflation (MI-E) device. Reproduced from Chatwin et al. *(2018) with permission.*

Traditional (active) physiotherapy techniques are not useful in this group once forced expiratory flows decrease below 160–200 $L \cdot min^{-1}$. In such cases, strategies to enhance maximal insufflation capacity (MIC) and enhance expiratory flows are indicated (figure 2.)

The presence of severe bulbar dysfunction or paralysis renders breath stacking ineffective. MIC enhancement, used regularly, is also a means of maintaining the range of movement in the lungs and chest wall. These techniques should be used along with strategies to enhance cough effectiveness: manually assisted coughing or mechanical insufflation–exsufflation.

Ventilatory function can be improved with careful positioning to optimise the effect of gravity on weak muscles, as can the use of abdominal binders for those with spinal cord injury (SCI).

In patients with SCI, exercise should be encouraged; respiratory muscle training and functional electrical stimulation may enhance muscle strength or vital capacity. Some patients with early progressive neuromuscular disease may still benefit from respiratory muscle training but this needs to be thoroughly discussed with patients and caregivers in view of prognosis and alternative treatment options. To date, evidence for inspiratory muscle training in this population (with the exception of SCI) is limited.

Patients with critical illness

The principles of care remain the same in critically ill patients as in other patients. Physiotherapists are crucial in providing early mobilisation in the ICU, and in providing rehabilitation after ICU, for the prevention and treatment of the common complications associated with prolonged bed rest: immobility and recumbence, including deconditioning, weakness and dyspnoea. Physiotherapy is also used to target specific respiratory problems, such as retained airway secretions, atelectasis and weaning failure (Gosselink *et al.*, 2008).

Further reading

- Bott J, *et al.* (2009). Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient. *Thorax*; 64: Suppl. 1, i1–i51.
- Boulding R, *et al.* (2016). Dysfunctional breathing: a review of the literature and proposal for classification. *Eur Respir Rev*; 25: 287–294.
- British Thoracic Society, *et al.* (2016). British guideline on the management of asthma: a national clinical guideline. Available from: www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2016/
- Bruton A, *et al.* (2018). Physiotherapy breathing retraining for asthma: a randomised controlled trial. *Lancet Respir Med*; 6: 19–28.
- Button BM, *et al.* (2016). Physiotherapy for cystic fibrosis in Australia and New Zealand: a clinical practice guideline. *Respirology*; 21: 656–667.
- Chatwin M, *et al.* (2018). Airway clearance techniques in neuromuscular disorders: a state of the art review. *Respir Med*; 136: 98–110.
- Gosselink R, *et al.* (2008). Physiotherapy for adult patients with critical illness: recommendations of the European Respiratory Society and European Society of Intensive Care Medicine Task Force on Physiotherapy for Critically Ill Patients. *Intensive Care Med*; 34: 1188–1199.
- Langer D, *et al.* (2009). A clinical practice guideline for physiotherapists treating patients with chronic obstructive pulmonary disease based on a systematic review of available evidence. *Clin Rehabil*; 23: 445–462.
- Muñoz G, *et al.* (2018). Long-term benefits of airway clearance in bronchiectasis: a randomised placebo-controlled trial. *Eur Respir J*; 51: 1701926.
- Perez-Bogerd S, *et al.* (2018). Short and long-term effects of pulmonary rehabilitation in interstitial lung diseases: a randomised controlled trial. *Respir Res*; 19: 182.
- Pitta F, *et al.* (2014). A core syllabus for post-graduate training in respiratory physiotherapy. *Breathe*; 10: 220–228.
- Polverino E, *et al.* (2017). European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J* 2017; 50: 1700629.
- Tang CY, *et al.* (2010). Chest physiotherapy for patients admitted to hospital with an acute exacerbation of chronic obstructive pulmonary disease (COPD): a systematic review. *Physiotherapy*; 96: 1–13.

Pulmonary rehabilitation

Thierry Troosters, Wim Janssens, Daniel Langer and Heleen Demeyer

Definition

Pulmonary rehabilitation is now a recognised therapy for patients with respiratory diseases. Its effectiveness is supported by countless randomised controlled trials. In 2013, the European Respiratory Society (ERS) and American Thoracic Society (ATS) defined pulmonary rehabilitation as 'a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies which include, but are not limited to, exercise training, education and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours'. This definition, although long, identifies the core components of a rehabilitation programme (Spruit, *et al.*, 2013). The statement also provides insight on the expected outcomes as well as the process followed throughout a rehabilitation programme. In an initial phase, a rehabilitation programme aims to assess and, where possible, restore the non-respiratory consequences of respiratory diseases (*i.e.* muscle weakness, depressive symptoms, poorly coping with the disease, impaired engagement in physical activities, nutritional deficits, *etc.*). Subsequently, or in parallel, the rehabilitation programme calls for the self-management of patients to engage in a healthy lifestyle in terms of physical activity, nutrition, smoking and coping. The rehabilitation team becomes the patient's coach. In the first phase, exercise training is a crucial part of the rehabilitation programme; later on, the focus can gradually shift towards more lifelong behavioural change. Whereas the science of the former has reached a very high standard, with a clear evidence base, the latter is still less well studied but is of equal importance. While most of the evidence, also discussed in this section, is present for COPD, pulmonary rehabilitation has also been proven to be effective in interstitial lung disease (Nakazawa *et al.*, 2017), pulmonary hypertension (Leggio *et al.*, 2018), CF (Gruet *et al.*, 2017), after lung transplantation (Langer *et al.*, 2012) or in patients treated for lung cancer (Cavalheri *et al.*, 2014).

Key points

- Pulmonary rehabilitation is an evidence-based treatment that improves exercise tolerance, health-related quality of life and symptoms in COPD.
- Programmes should be tailored to the patient in terms of content, location, duration, frequency and exercise training.
- In order for the effects to be durable, patients' physical activity levels should be higher after rehabilitation than before.

In these conditions, programmes may need disease-specific modifications. In patients with pulmonary hypertension, for example, training intensity is typically somewhat lower, in patients with CF individual training rather than group training programmes may be used or for patients with interstitial lung disease the content of the educational programme may need to be adapted. For all patients, however, the same general concepts apply.

Here, we will review the different aspects of the definition of pulmonary rehabilitation:

- the evidence base and anticipated effects;
- the selection of patients;
- the individualisation of the programme; and
- the mechanisms through which the programme works (reversing the systemic, extrapulmonary consequences).

Importantly, pulmonary rehabilitation may be an integrated part of other care plans for COPD patients, such as pharmacotherapy, self-management programmes, lung transplantation programmes, NIV or smoking cessation programmes. Recent studies have also formally assessed how exercise training can contribute to the effects of increasingly more complex programmes, such as self-management behaviour modification to increase physical activity and pharmacotherapy.

The evidence base for pulmonary rehabilitation

Several reviews have summarised the evidence for pulmonary rehabilitation (McCarthy *et al.*, 2015) and practice guidelines or statements are available (Spruit *et al.*, 2013; Langer *et al.*, 2009). Therefore, a comprehensive review of all evidence for the effectiveness of pulmonary rehabilitation is beyond the scope of this short review.

Briefly, in patients with COPD, pulmonary rehabilitation improves physical as well as mental fitness, health-related quality of life and symptoms and these benefits are perceived by patients (*e.g.* benefits exceed the minimally important difference). Other benefits include a reduction in utilisation of healthcare resources in patients with excessive use of healthcare as well as better self-management skills.

Physiological improvements

When whole body exercise training (cycling, walking, water based training) is offered at adequate intensity and according to the principles mentioned below, clinically important improvements in exercise tolerance and functional exercise capacity are found. Endurance time nearly doubles in programmes that applied proper training programmes. These effects are seen on top of the effects observed with pharmacotherapy. Therefore, the pharmacologic approach and exercise training are complementary approaches to improve exercise tolerance in patients with lung disease. Besides cardiorespiratory fitness, exercise training also ameliorates skeletal muscle function. When respiratory muscle training is added, additional benefits on respiratory muscle function and symptoms of dyspnoea can be expected. This specific training modality is added only when respiratory weakness is present. In fact, exercise training is currently the only technique available to reverse the skeletal muscle deconditioning that is often observed in patients with chronic respiratory disorders (Maltais *et al.*, 2014). When resistance training is offered, additional benefits on outcomes like skeletal muscle strength are to be expected. This may be crucially important in patients suffering from skeletal muscle weakness.

Psychological improvements

A significant proportion of patients referred for pulmonary rehabilitation suffer from psychiatric morbidity. Anxiety and depression are the most common problems and are a negative prognostic factor in patients with COPD, particularly in patients who suffered from exacerbations. A meta-analysis showed the benefit of multidisciplinary pulmonary rehabilitation on mood (Coventry *et al.*, 2013). It is not very clear which components are essential to enhance the psychological well-being of patients. Exercise training *per se* plays a role in improving mental health. Cognitive behaviour therapy can also contribute to reduced anxiety or depressive symptoms (Heslop-Marshall *et al.*, 2018) and it cannot be excluded that the group dynamic of being involved in rehabilitation also improves psychological and social well-being. In patients referred to our rehabilitation programme, depressive symptoms were present in 42% of patients and symptoms compatible with anxiety in 38% of patients (Trappenburg *et al.*, 2005). Clearly, one has to take into account that effects on these variables are only to be expected if patients do have symptoms of depression and/or anxiety. Hence, the relatively small effect size reported in the meta-analysis may be induced by the dilution of the depressed patients in the larger patient pool.

Physical activity

The amount of activity patients carry out in their daily life is an important outcome for rehabilitation. Enhancing physical activity is now recognised as one of the most important goals of pulmonary rehabilitation. The ‘systemic consequences’ of COPD, such as cardiovascular morbidity, muscle weakness and osteoporosis, originate, to a large extent, directly or indirectly from living an inactive lifestyle. The effect pulmonary rehabilitation programmes have on physical activity levels have been variable and are surely less certain than the effects on exercise tolerance. While statistically significant, effects remain somewhat disappointing. When programmes are equipped with behaviour modification support, effects are likely to be somewhat better (Lahham *et al.*, 2016) albeit not guaranteed. Changing physical activity may not simply follow the increased exercise capacity. In fact, enhanced physical activity can be seen in the absence of enhanced exercise tolerance as is observed with behaviour change programmes outside the context of pulmonary rehabilitation and enhanced exercise tolerance can be observed without dramatic changes in physical activity. Indeed, physical activity levels are a complex integration of the exercise capacity of patients, their willingness to use that acquired capacity in a more physically active lifestyle and their interaction with the (social) environment offering opportunities for physical activity. In the past decade, appealing new strategies have been developed that may potentially help to increase the effects of classical rehabilitation on physical activities. Coaching programmes that integrate concepts known in successful behaviour change models have been applied successfully in COPD. It should be mentioned, however, that even when these strategies are applied, it is difficult to enhance physical activity if patients have a very low exercise tolerance or lack motivation for behaviour change. The current state-of-the-art suggests that in patients with sufficient exercise tolerance (6-min walking distance >350 m), a programme providing direct feedback to patients and goal setting using an activity monitor may be a good approach to enhance physical activity. It seems important that patients also find activities (goal setting) that involve physical activity engagement which they like and are willing to pursue after the programme. It is fair to say that more research is needed to identify the optimal strategies to achieve physical activity benefits.

Utilisation of healthcare resources

An important spin-off of pulmonary rehabilitation is the reduction in the utilisation of healthcare recourses. The most important source of utilisation of healthcare recourses is hospital admissions. Direct prospective evidence of a reduction in days spent in hospital is available (Griffiths *et al.*, 2000). Recent systematic reviews also confirmed the benefits of pulmonary rehabilitation in postponing hospital admissions when patients are enrolled in pulmonary rehabilitation (Puhan *et al.*, 2016; Moore *et al.*, 2016).

A comprehensive intervention: programme content

As indicated above, programmes need to be individualised, aim to improve the systemic consequences (physiological and psychological) of the underlying respiratory disease, and guide the patients and their families towards a long-term change in physical activity and self-management behaviour. Several options are possible in terms of which disciplines should contribute to the programme, location, duration and frequency. These are briefly summarised in table 1. A comprehensive review is provided elsewhere (Spruit *et al.*, 2013). Studies that compared different modalities of rehabilitation head-to-head are scarce and no unequivocal preference has been reported. Studies that compared the effectiveness of hospital-based outpatient rehabilitation to rehabilitation at home (or in primary care/community) found no differences between them in short-term outcomes. None of the studies had specifically

Table 1. Choices to be made when prescribing pulmonary rehabilitation

Aspects to be individualised	Possible choices or options
Involved disciplines	Chest physicians, physiotherapists, nurses, exercise specialists, occupational therapists, psychologists/behavioural coaches, social workers, dieticians, general practitioners, family members or care givers
Location	Rehabilitation centre: in-patient, outpatient or home based but with close connection to a specialised centre Community based: out-patient in centre or primary care office Home-based supervised by primary care team Direct, face to face Remote (telerehabilitation)
Duration	≥8 weeks, but longer is typically more desirable
Frequency	A minimum of three sessions per week of which two are supervised
Exercise training component	Exercise modalities (walking, cycling, upper limbs, *etc.*) Exercise intensity preferably high (Borg symptom rating 4 to 6/10) Exercise type: interval, endurance, resistance Additional interventions: inspiratory muscle training, oxygen therapy, NIV, neuromuscular electrical stimulation
Physical activity behaviour	Motivational counselling, use of step counter, enrolment in regular activity 'class' (*e.g.* walking group)

selected patients into one setting or the other, based on patient preference or patient characteristics. More research is needed to evaluate the criteria for assigning patients to a specific form of rehabilitation. In addition, it remains unclear to what extent home or centre-based rehabilitation results in more enduring effects. More recently, rehabilitation forms are being developed where patients can follow the programme from home, but supervision is provided remotely *via* telemedicine applications. Evolution in technology and e-literacy make these evolutions possible, but the impact on healthcare systems and uptake by healthcare systems remains anecdotal.

The exercise training component is essential, and the programme needs to be individualised in terms of exercise modalities, specificity of the training, the training intensity and specific inspiratory muscle training (if indicated, *i.e.* inspiratory muscle weakness and symptoms of dyspnoea). In order to obtain significant physiological improvements in skeletal muscle function, it is important to train patients at an intensity that is high relative to the maximum capacity of the patients. Recently, programmes eliciting more significant skeletal muscle fatigue were related to better training effects in terms of functional exercise tolerance and reduction of symptoms (Burtin *et al.*, 2012). In order to combine an effective training programme with patient comfort, clinicians have the choice of several exercise training modalities. These include high-intensity endurance training (Casburi *et al.*, 1991), interval training (Beauchamp *et al.*, 2010) and resistance training (Iepsen *et al.*, 2015). In patients with severe skeletal muscle impairment, neuromuscular electrical stimulation can help to enhance skeletal muscle force. The duration of an exercise training programme is generally believed to be minimally 8 weeks and a minimum of three sessions is needed, although, admittedly, solid evidence as to the optimal duration is still missing (Spruit *et al.*, 2013). One of these sessions can be conducted outside the formally supervised setting by the patients, provided that the session is comparable in terms of duration and intensity to the supervised sessions.

Maintaining the effects of pulmonary rehabilitation

When exercise training programmes are interrupted, the effects of the exercise programme will disappear. Hence, it is important that attention is given to maintain exercise and physical activity routines when a rehabilitation programme comes to an end. This may be easier to achieve when the original rehabilitation programme is somewhat longer, allowing time to achieve a desirable change of behaviour. While firm evidence is currently lacking, the maintenance of regular exercise may prevent future deconditioning in patients (Beauchamp *et al.*, 2013). The best or most cost-efficient way of offering such programmes is not well studied. In order for these programmes to be feasible, they likely need to be conducted in the community. In complex patients, however, some follow-up from experts in the rehabilitation centre may be required. Training with telemonitoring could perhaps provide opportunities in the future.

Specific attention should be given to patients who suffer from exacerbations, as these events acutely reduce muscle force and functional exercise capacity. Although it seems intuitively useful, there is currently little evidence for a short ‘booster’ programme after a hospital admission to reinforce benefits of prior rehabilitation (Carr *et al.*, 2009). Nevertheless, such repeat programmes are capable of significant improvements of symptoms and exercise tolerance

Patient selection: patients with systemic consequences

The 2006 definition of pulmonary rehabilitation included the goals of rehabilitation: pulmonary rehabilitation is ‘designed to reduce symptoms, optimise functional status, increase participation, and reduce healthcare costs through stabilising or reversing systemic manifestations of the disease' (Nici *et al.*, 2006). From this, it followed that the ideal candidate for rehabilitation is symptomatic, has impaired functional status and participation, high utilisation of healthcare recourses, and suffers from the 'systemic consequences of COPD'. Hence, the selection of patients should not be performed based on lung function, but rather on the proper assessment of the extrapulmonary consequences of COPD found to be reversible with rehabilitation: symptoms, functional status, the levels of participation in daily life and health-related quality of life. Other factors, such as age, sex and smoking status, are not important predictors of the outcome of rehabilitation. It is important that patients are screened for pulmonary rehabilitation after establishing optimal pharmacotherapy. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) proposes rehabilitation in all symptomatic patients and in those with exacerbations (GOLD groups B–D) (Vogelmeier *et al.*, 2017). While being screened for rehabilitation, patients can also be considered for other programmes, such as lung transplantation or lung volume reduction, NIV support or oxygen therapy. Such programmes are not exclusion criteria for pulmonary rehabilitation. On the contrary, pulmonary rehabilitation is often strongly recommended for these patients. Figure 1 gives an overview of the selection process for patients with COPD and the design of the programme.

Extrapulmonary consequences of COPD

In the context of exercise training, the most important systemic consequence of COPD is skeletal muscle dysfunction. In clinical practice, this can be assessed by skeletal muscle force or local skeletal muscle endurance, which is often even

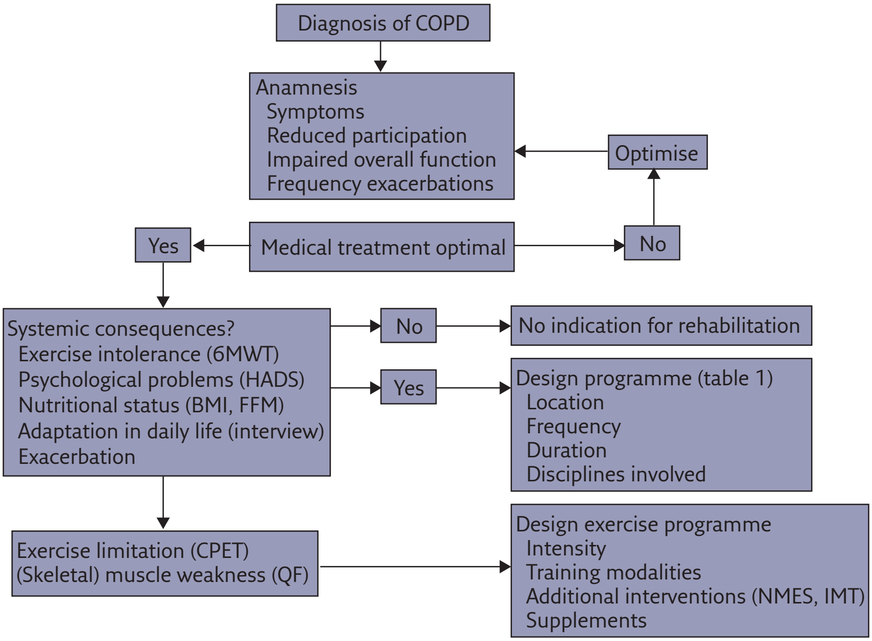

Diagnosis of COPD
Anamnesis
Symptoms
Reduced participation
Impaired overall function
Frequency exacerbations
Optimise
Yes
Medical treatment optimal
No
Systemic consequences?
Exercise intolerance (6MWT)
Psychological problems (HADS)
Nutritional status (BMI, FFM)
Adaptation in daily life (interview)
Exacerbation
No
No indication for rehabilitation
Yes
Design programme (table 1)
Location
Frequency
Duration
Disciplines involved
Exercise limitation (CPET)
(Skeletal) muscle weakness (QF)
Design exercise programme
Intensity
Training modalities
Additional interventions (NMES, IMT)
Supplements

Figure 1. Flow chart for referral to pulmonary rehabilitation programmes. 6MWT: 6-min walk test; HADS: hospital anxiety and depression scale; FFM: fat-free mass; CPET: cardiopulmonary exercise test; QF: quadriceps force; NMES: neuromuscular electrical stimulation; IMT: inspiratory muscle training.

more affected. Skeletal muscle dysfunction can be observed in all stages of chronic respiratory disease. In patients with newly detected GOLD stage II COPD, van Wetering *et al.* (2008) suggested quadriceps weakness occurred in 28% of the patients. In these patients, quadriceps force was related to exercise capacity, as was shown previously in more severe patients (Gosselink *et al.*, 1996). In milder patients (FEV1 >80% predicted), muscle weakness was actually a predictor of physical activity levels (Shrikrishna *et al.*, 2012). Reversal of skeletal muscle dysfunction is an important goal of the exercise training component of a rehabilitation programme and, hence, patients suffering from skeletal muscle weakness are particularly good candidates for exercise training. Skeletal muscle strength can be improved particularly effectively by including resistance training exercises in the sessions. When successful, muscle force does increase and muscle oxidative capacity is enhanced and almost normalised.

More research is needed on pharmacological interventions that may assist pulmonary rehabilitation in order to restore muscle function more effectively. A comprehensive review on skeletal muscle dysfunction in COPD is available in the ERS/ATS statement on skeletal muscle dysfunction in COPD (Maltais *et al.*, 2014). It is important to recognise that muscle dysfunction is not only a feature of COPD, it also affects patients with other chronic respiratory conditions like CF or interstitial lung disease.

Impaired exercise tolerance and functional exercise capacity are the result of the pulmonary and systemic consequences of COPD. In the context of pulmonary rehabilitation, exercise tolerance is best assessed before the programme using an incremental exercise test. This will help guide the exercise training programme in terms of its intensity, training modalities and safety. Functional exercise capacity is best assessed using field tests such as the 6-min walk test. For this test, reference values exist and benchmark improvements for programme quality, and clinical and statistical importance have been reported. The ERS/ATS technical standard on field walking tests summarises the most important features (Holland *et al.*, 2014). When a patient’s exercise tolerance is not abnormal, the indication for exercise training is questionable.

Another important extrapulmonary consequence of COPD is the derangement of the body composition. Both obesity, as a consequence of an inactive lifestyle, and cachexia, as observed in other chronic inflammatory disorders, are important to pick up on and treat in pulmonary rehabilitation programmes. Obese patients may experience less dyspnoea for a given oxygen consumption compared to non-obese patients due to a favourable mechanical effect of obesity on the operating lung volumes. Nevertheless, obesity (defined as a BMI >30 $kg \cdot m^{-2}$) will limit the functional abilities of patients with limited ventilatory capacity, as it increases oxygen consumption and hence the ventilatory need during exercise against gravity. Cachexia, an involuntary loss of fat-free mass, inevitably leads to skeletal muscle weakness. It is a complex problem and its origin is not yet fully understood. Energy imbalance, disuse atrophy, hormonal imbalance, chronic hypoxia, accelerated ageing and systemic inflammation have been discussed as potential factors contributing to cachexia (Schols *et al.*, 2014). The treatment of cachexia is an important aspect of rehabilitation in patients with COPD and requires individualised interventions by nutritional specialists. In order to appropriately assess this aspect, body composition should be assessed using dual-energy X-ray absorptiometry or bioelectrical impedance measurements (Schols *et al.*, 2014).

Symptoms

The most disabling symptom in COPD is clearly shortness of breath. Patients report dyspnoea, particularly during exercise or activity as a significant burden. Another important symptom is fatigue. Symptoms can be assessed during exercise using Borg symptom scores or patient experiences during activities of daily living using specific patient reported outcome measures (Lareau *et al.*, 1998; Garrod *et al.*, 2000; Gimeno-Santos *et al.*, 2015).

Physical activity

The participation of patients in daily activities is not easily assessed. The methodology to assess physical activity was reviewed by an ERS task force (Watz *et al.*, 2014). Physical activity monitors have found their way to the clinical arena and validation studies of several monitors are available (van Remoortel *et al.*, 2012). In the future, it is likely that benchmark values for physical activity will become available for patients with COPD. As indicated above, patients not meeting current guidelines on healthy physical activity (30 min of moderately intense exercise, 5 days per week) can be considered candidates for pulmonary rehabilitation where the focus lies on improving the physical activity lifestyle of the patient.

Severe exacerbations

Patients with COPD who have been hospitalised with an acute exacerbation are particularly good candidates for enrolment in pulmonary rehabilitation programmes. Recent ERS guidelines advocate enrolling patients who were hospitalised in a pulmonary rehabilitation programme within 4 weeks after discharge (Wedzicha *et al.*, 2017). Patients suffering from exacerbations have acutely lost muscle force, functional exercise tolerance and health-related quality of life as the result of an exacerbation. Physical activity levels are also dramatically low during the hospital admission and for at least up to 1 month afterwards (Pitta *et al.*, 2006). That observation prompted investigators to look at the effects of muscle activation during the hospitalisation phase by means of resistance training (Troosters *et al.*, 2010) or neuromuscular electrical stimulation (Abdellaoui *et al.*, 2011). In addition, it is well known that patients who had a hospital admission for COPD are very likely to face new hospital admissions in the year following the previous admission, imposing a high burden of healthcare cost. The risk of re-admission is particularly high in patients who remain inactive after a hospitalisation. In these patients, the rehabilitation programme may need significant modification. The emphasis should be on acquiring appropriate self-management skills and programmes should be sufficiently long to prevent subsequent admissions. The exercise training programme may need to be adapted to more severe ventilatory and/or skeletal muscle limitation, using resistance training or interval training at high intensities, when needed with oxygen supplements. Clearly, these patients may impose a higher burden on the rehabilitation team and drop-out from the programme is a particularly important problem. However, when successful, entering a pulmonary rehabilitation programme is probably the most effective way to prevent, or delay subsequent admissions.

Conclusion

Pulmonary rehabilitation is an evidence-based intervention for patients with chronic respiratory disorders. It is individually tailored to the needs of patients, both in terms of the programme structure and its components. The aim of the rehabilitation programme is to lead to an endurable change in physical activity and self-management behaviour. Although the short-term effects of rehabilitation are well known, the long term effects, as well as the effects on physical activity are not always guaranteed. Further research should focus on the strategies to ensure long-term benefits for patients with COPD. Further knowledge on the processes underlying an enduring shift in lifestyle, as well as better understanding of the pathophysiological mechanisms leading to the systemic consequences of COPD and its treatments, may lead to major advances in the future.

Further reading

- Abdellaoui A, *et al.* (2011). Skeletal muscle effects of electrostimulation after COPD exacerbation: a pilot study. *Eur Respir J*; 38: 781–788.
- Beauchamp MK, *et al.* (2010). Interval *versus* continuous training in individuals with chronic obstructive pulmonary disease – a systematic review. *Thorax*; 65: 157–164.
- Beauchamp MK, *et al.* (2013). Systematic review of supervised exercise programs after pulmonary rehabilitation in individuals with COPD. *Chest*; 144: 1124–1133.
- Burtin C, *et al.* (2012). Effectiveness of exercise training in patients with COPD: the role of muscle fatigue. *Eur Respir J*; 40: 338–344.
- Carr SJ, *et al.* (2009). Pulmonary rehabilitation after acute exacerbation of chronic obstructive pulmonary disease in patients who previously completed a pulmonary rehabilitation program. *J Cardiopulm Rehabil Prev*; 29: 318–324.
- Casaburi R, *et al.* (1991). Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis*; 143: 9–18.
- Cavalheri V, *et al.* (2014). Exercise training for people following lung resection for non-small cell lung cancer – a Cochrane systematic review. *Cancer Treat Rev*; 40: 585–594.
- Coventry PA, *et al.* (2013). The effect of complex interventions on depression and anxiety in chronic obstructive pulmonary disease: systematic review and meta-analysis. *PLoS One*; 8: e60532.
- Garrod R, *et al.* (2000). Development and validation of a standardized measure of activity of daily living in patients with severe COPD: the London Chest Activity of Daily Living scale (LCADL). *Respir Med*; 94: 589–596.
- Gimeno-Santos E, *et al.* (2015). The PROactive instruments to measure physical activity in patients with chronic obstructive pulmonary disease. *Eur Respir J*; 46: 988–1000.
- Gosselink R, *et al.* (1996). Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med*; 153: 976–980.
- Griffiths TL, *et al.* (2000). Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet*; 355: 362–368.
- Gruet M, *et al.* (2017). Peripheral muscle abnormalities in cystic fibrosis: etiology, clinical implications and response to therapeutic interventions. *J Cyst Fibros*; 16: 538–552.
- Heslop-Marshall K, *et al.* (2018). Randomised controlled trial of cognitive behavioural therapy in COPD. *ERJ Open Res*; 4: 00094–2018.
- Holland AE, *et al.* (2014). An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J*; 44: 1428–1446.
- Iepsen UW, *et al.* (2015). A combination of resistance and endurance training increases leg muscle strength in COPD: an evidence-based recommendation based on systematic review with meta-analyses. *Chron Respir Dis*, 2015; 12: 132–145.
- Lahham A, *et al.* (2016). Exercise training alone or with the addition of activity counseling improves physical activity levels in COPD: a systematic review and meta-analysis of randomized controlled trials. *Int J Chron Obstruct Pulmon Dis*; 11: 3121–3136.
- Langer D, *et al.* (2009). A clinical practice guideline for physiotherapists treating patients with chronic obstructive pulmonary disease based on a systematic review of available evidence. *Clin Rehabil*; 23: 445–62.
- Langer D, *et al.* (2012). Exercise training after lung transplantation improves participation in daily activity: a randomized controlled trial. *Am J Transplant*; 12: 1584–1592.

- Lareau SC, *et al.* (1998). Development and testing of the modified version of the pulmonary functional status and dyspnea questionnaire (PFSDQ-M). *Heart Lung*; 27: 159–168.
- Leggio, M, *et al.* (2018). Pulmonary hypertension and exercise training: a synopsis on the more recent evidences. *Ann Med*; 50: 226–233.
- Maltais F, *et al.* (2014). An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 189: e15–e62.
- McCarthy B, *et al.* (2015). Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*; 2015: CD003793.
- Moore E, *et al.* (2016). Pulmonary rehabilitation as a mechanism to reduce hospitalizations for acute exacerbations of COPD: a systematic review and meta-analysis. *Chest*; 150: 837–859.
- Nakazawa, A, *et al.* (2017). Current best practice in rehabilitation in interstitial lung disease. *Ther Adv Respir Dis*; 11: 115–128.
- Nici L, *et al.* (2006). American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med*; 173: 1390–1413.
- Pitta F, *et al.* (2006). Physical activity and hospitalization for exacerbation of COPD. *Chest*; 129: 536–544.
- Puhan MA, *et al.* (2016). Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*; 12: CD005305.
- Schols AM, *et al.* (2014). Nutritional assessment and therapy in COPD: a European Respiratory Society statement. *Eur Respir J*; 44: 1504–1520.
- Shrikrishna D, *et al.* (2012). Quadriceps wasting and physical inactivity in patients with COPD. *Eur Respir J*; 40: 1115–1122.
- Spruit, MA, *et al.* (2013). An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*, 2013; 188: e13–e64.
- Trappenburg JC, *et al.* (2005). Psychosocial conditions do not affect short-term outcome of multidisciplinary rehabilitation in chronic obstructive pulmonary disease. *Arch Phys Med Rehabil*; 86: 1788–1792.
- Troosters T, *et al.* (2010). Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 181: 1072–1077.
- van Remoortel H, *et al.* (2012). Validity of activity monitors in health and chronic disease: a systematic review. *Int J Behav Nutr Phys Act*; 9: 84.
- van Wetering CR, *et al.* (2008). Systemic impairment in relation to disease burden in patients with moderate COPD eligible for a lifestyle program. Findings from the INTERCOM trial. *Int J Chron Obstruct Pulmon Dis*; 3: 443–451.
- Vogelmeier CF, *et al.* (2017). Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: gold executive summary. *Eur Respir J*; 49: 1700214.
- Watz H, *et al.* (2014). An official European Respiratory Society statement on physical activity in COPD. *Eur Respir J*, 2014; 44: 1521–1537.
- Wedzicha JA, *et al.* (2017). Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*; 49: 1600791.

Palliative care

Sylvia Hartl

Palliative care is aimed at the prevention and relief of symptoms and the improvement of the quality of life according to the needs of the patients and their families in parallel with curative treatment. It includes all methods for the control of breathlessness, pain, social, psychological and spiritual distress, as well as advanced care planning along the disease trajectories including support during the process of dying and bereavement care.

In addition to cancer patients, in chronic respiratory diseases like COPD, CF, interstitial lung diseases and pulmonary hypertension, patients may suffer from the same needs for palliative care during their disease trajectory. Nevertheless, only a small proportion (*e.g.* <10% in COPD) are offered palliative care by their physicians.

Implementation

Palliative care is feasible for all progressive chronic or life-threatening diseases in parallel to curative therapies and is continued to support patients' preferences for the maintenance of quality of life including easing the process of dying (table 1).

For patients who are able to make decisions, it is important to discuss their needs together with their families at an appropriate time in their disease trajectory. Advance care planning enables individuals to define goals and preferences for future medical treatment and care, to discuss these goals and preferences with family and healthcare providers, and to record and review these preferences if appropriate.

Advance care planning helps the physicians and caregivers to better understand the patients will and to treat chronic respiratory diseases accordingly. It not only comprises palliative methods but also supports life sustaining measures. Other than in former perceptions of palliation when end of life decisions were the main aim, the heavy burden of symptoms in earlier disease stages and the long course of suffering

Key points

- Palliative care should be evaluated in chronic respiratory diseases with a high burden of symptoms in parallel to curative treatment.
- Palliative care is a multidisciplinary approach and needs teams of specialists with experience and training in palliative care.
- Advance care planning enables individuals to define goals and preferences for future medical treatment and care, to discuss these goals and preferences with family and healthcare providers, and to record and review these preferences if appropriate.

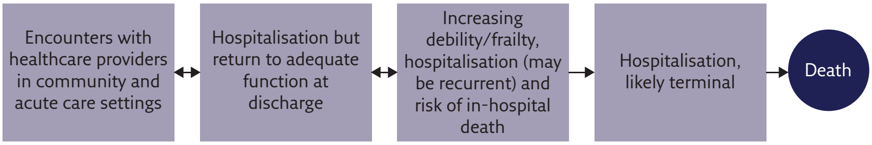
in chronic respiratory diseases has changed the perception of the usefulness of treatment interventions.

The provision of competent caregivers is part of the implementation of palliative care. The evaluation for palliative care includes the following.

Physical support

Evaluation of breathlessness and general physical performance including fatigue and pain management offering pharmacological and non-pharmacological treatment options.

- Opioids can be helpful in breathlessness and pain management. Drug dosage for breathlessness relief is often lower than for pain management and has to be titrated to the level of satisfaction. Pain management in diseases other than cancer often uses drugs like non-steroidal antirheumatics or paracetamol before using opioids due to better management of side-effects. If necessary, opioids can be used in even higher dosages in close observation of the management of side-effects, like constipation or psychiatric symptoms of confusion or drowsiness.
- Panic attacks and depression are often related to refractory breathlessness and terminal respiratory failure and can be alleviated by anxiolytic and antidepressant drugs. The effects have to be observed closely and discussed with the patient. In every case psychological counselling and coaching must accompany any drug therapy.
- Nutrition supplements in some patients prevent weight loss and malnutrition and pulmonary cachexia. They help to postpone fatigue depending on what preference the patient set up as a goal. Fatigue is induced by breathlessness and low-calorie intake, but is also supported by depression and low physical activity during disease


Encounters with healthcare providers in community and acute care settings
Hospitalisation but return to adequate function at discharge
Increasing debility/frailty, hospitalisation (may be recurrent) and risk of in-hospital death
Hospitalisation, likely terminal
Death

Diagnosis/progression of life-limiting illness

- Acknowledgement of uncertainty of prognosis
- Begin advance care planning process in the community, outpatient setting or hospital
- Care coordination and liaison with community services (*e.g.* general practice, home-based and residential aged care services)
- Ongoing active treatment ± palliative approach for symptom management and psychosocial support

Likely to die soon (medium term but timing may be uncertain)

- Goal setting and advance care planning
- Palliative approach for symptom management, and psychosocial and family support (treating team ± specialist team)
- Clear management planning (including limitations of medical treatment) on admission and/or after episodes of acute deterioration
- Care coordination and liaison with community services (*e.g.* home-based and residential aged care services)
- Medication review

Dying (short term but timing may be uncertain)

- Review by senior clinician
- Goal setting and advanced care planning
- Clear management planning (including limitations of medical treatment) on admission and/or after episodes of acute deterioration
- Interventions for symptom control, meeting spiritual and cultural needs, family support, *etc.*
- Medication review
- Provision of terminal care
- Bereavement care for family

Figure 1. Interaction between deterioration in the patient, health service usage and timing for medical planning. Reproduced from the Australian Commission.

progression. Therefore, a multi-interventional approach of rehabilitation, nutrition and psychological counselling might be most effective.

- Non-pharmacological interventions should always be offered.
- Rehabilitation to prevent deterioration and restore the physical function is not only crucial for quality of life but is also life sustaining.
- Methods like noninvasive ventilation and long-term oxygen therapy might effectively improve physical performance and lower the burden of the high work of breathing when appropriately evaluated and applied. It is feasible to have a trial period and select responders. Caregivers have to be trained well for home therapy.
- Lung volume reduction is another option for selected patients with COPD and can substantially improve breathlessness and physical capacity for a while.

Psychological support

Like cognitive behavior therapy, psychological support can be offered successfully in many patients early in the course of the disease. It may be effective in treating breathlessness but also in coping with emotional distress and superimposed psychiatric symptoms.

Spiritual coaching

This depends on the spiritual background of the patient, and should be evaluated for the mutual understanding of professional caregivers and patients and family's perception of disease, as well as their expectations of the dying process.

Advance care planning

This allows the discussion of all measures that can be helpful to support patients and family's preferences during the changing trajectories of the disease (figure 1). Therefore, an escalation or limitation of certain treatment options can be discussed within advance care planning. The frequency of re-evaluation depends on the expected needs which are often difficult to predict, not only due to the underlying disease but also driven by comorbidities. Advance care planning should always be initiated in a stable phase of disease.

Terminal support

Terminal support for chronic respiratory failure and imminent dying is often not easy to foresee and depends a great deal on the expertise of the treatment team. Timely communication about end of life scenarios to the patients and their relatives will facilitate the access to adequate care. In this phase, concomitant treatment is often re-evaluated for withdrawal or withholding of measures, if applicable.

Table 1. Key processes of palliative care

Palliative care means routine evaluation for:
Symptom control: breathlessness, fatigue, pain and general physical performance status
Stress reduction: anxiety, depression, beliefs and expectations
Advance care planning: manage disease progress and critical deterioration
Terminal support: chronic respiratory failure and imminent dying
Bereavement: not abandonment and closure after death

Bereavement

Caregivers who are highly involved in the patients suffering and needs are often not sufficiently evaluated for their personal needs.

- Changes from active treatment to best supportive care only is also changing the role of the family caregivers. It can be perceived as abandonment of the patient and results in the uncertainty of still having access to the best 'treatment'.
- After death, palliative teams should allow the patients caregivers to close the relationship with the team.

Further reading

- Ahmadi Z, *et al.* (2017). Palliative oxygen for chronic breathlessness: what new evidence? *Curr Opin Support Palliat Care*; 11: 159–164.
- Australian Commission on Safety and Quality in Health Care. National Consensus Statement: Essential Elements for Safe and High-Quality End-Of-Life Care. Available from: www.safetyandquality.gov.au/wp-content/uploads/2015/05/National-Consensus-Statement-Essential-Elements-forsafe-high-quality-end-of-life-care.pdf Date last accessed: May 24, 2019. Date last updated: 2015.
- Back AL, *et al.* (2009). Abandonment at the end of life from patient, caregiver, nurse, and physician perspectives: loss of continuity and lack of closure. *Arch Intern Med*; 169: 474–479.
- Ekstrom M, *et al.* (2016). Prevalence of sudden death in palliative care: data from the Australian palliative care outcomes collaboration. *J Pain Symptom Manage*; 52: 221–227.
- Gomez-Batiste X, *et al.* (2017). Comprehensive and integrated palliative care for people with advanced chronic conditions: an update from several European initiatives and recommendations for policy. *J Pain Symptom Manage*; 53: 509–517.
- Iyer AS, *et al.* (2019). A formative evaluation of patient and family caregiver perspectives on early palliative care in COPD across disease severity. *Ann Am Thorac Soc*; https://doi.org/10.1513/AnnalsATS.201902-112OC.
- Johnson MJ, *et al.* (2012). Gaps in the evidence base of opioids for refractory breathlessness. A future work plan? *J Pain Symptom Manage*; 43: 614–624.
- Johnson MJ, *et al.* (2013). The evidence base for oxygen for chronic refractory breathlessness: issues, gaps, and a future work plan. *J Pain Symptom Manage*; 45: 763–775.
- Kreuter M, *et al.* (2017). Palliative care in interstitial lung disease: living well. *Lancet Respir Med*; 5: 968–980.
- Maddocks M, *et al.* (2017). Palliative care and management of troublesome symptoms for people with chronic obstructive pulmonary disease. *Lancet*; 390: 988–1002.
- Narsavage GL, *et al.* (2017). The potential of palliative care for patients with respiratory diseases. *Breathe*; 13: 278–289.
- Rietjens JAC, *et al.* (2017). Definition and recommendations for advance care planning: an international consensus supported by the European Association for Palliative Care. *Lancet Oncol*; 18: e543–e551.
- Scheerens C, *et al.* (2018). Comparing the use and timing of palliative care services in COPD and lung cancer: a population-based survey. *Eur Respir J*; 51: 1702405.

Oxygen therapy

Anita K. Simonds

Acute oxygen therapy

Acute oxygen therapy is indicated to improve oxygen delivery in situations of cardiac and respiratory compromise, acute severe hypotension, low cardiac output states in the presence of metabolic acidosis, and when S_{aO_2} is <90%. In respiratory conditions, oxygen therapy is prescribed to correct hypoxaemia, rather than to reduce breathlessness, and so should always be titrated to a target S_{aO_2} or blood gas measurements. In acutely ill patients, high-concentration oxygen therapy should be prescribed to correct S_{aO_2} to 94–98%. In those with hypercapnic respiratory failure or at risk of ventilatory decompensation (*e.g.* severe COPD, neuromuscular disease, obesity hypoventilation syndrome and chest wall disorders), a target S_{aO_2} of 88–92% should be the aim. If this cannot be achieved without progressive acidosis and hypercapnia, ventilatory support should be added. Indeed, in acute hypercapnic ventilatory failure, ventilatory support is usually the treatment of choice.

In emergency situations, oxygen therapy can be delivered by a high-concentration reservoir mask at a flow rate of 15 $\text{L}\cdot\text{min}^{-1}$. In hypercapnic patients, controlled oxygen therapy delivered *via* 28% and 24% Venturi masks can be used. All acute hypoxaemic patients require regular or continuous assessment by oximetry to ensure hypoxaemia has been corrected and that the flow rate is still appropriate. Blood gas measurements are indicated if there is deterioration in S_{aO_2}, features of carbon dioxide retention, such as drowsiness or flap, metabolic conditions, or low cardiac output state. There is no indication to overcorrect oxygenation as hyperoxia may decrease cardiac output and increase systemic vascular resistance, although effects vary between different disease conditions.

Key points

- Oxygen therapy is prescribed to correct hypoxaemia and should thus be titrated to S_{aO_2}.
- In acutely hypoxaemic patients, oxygen should be delivered to correct S_{aO_2} to 94–98%.
- In those with hypercapnic respiratory failure or at risk of ventilatory decompensation, a target of S_{aO_2} of 88–92% should be the aim.
- High-flow nasal cannulae therapy may be better tolerated by acutely hypoxaemic patients and is noninferior to NIV, depending on the underlying condition.

Long-term oxygen therapy

Chronic hypoxaemia occurs either due to ventilation–perfusion mismatch, alveolar hypoventilation or diffusion problems in chronic lung disease; in some conditions (*e.g.* COPD), all factors may be present. Long-term oxygen therapy (LTOT) is used to correct hypoxaemia diurnally and nocturnally in the majority of patients. In COPD, LTOT increases survival, reduces polycythaemia and, in some patients, may improve sleep quality and/or neuropsychiatric symptoms. In individuals with chronic ventilatory failure due, for example, to chest wall disease, the first-line treatment is assisted ventilation (*e.g.* NIV).

Patients should be assessed for LTOT in the presence of the features shown in table 1.

LTOT is prescribed for >15 h a day, *e.g. via* concentrator, to correct S_{aO_2} to ≥90% in those patients listed in table 2.

The indications for LTOT are based on trials published over 35 years ago. The more recent LOTT trial of long-term supplemental oxygen in COPD patients with moderate resting or ambulatory desaturation (S_{aO_2} 89–93%) showed no beneficial impact on survival, first hospitalisation or secondary end-points including quality of life. Patients with isolated nocturnal desaturation have not been extensively investigated in large trials. In this subgroup it would seem sensible to establish using a sleep study whether an additional problem such as OSA is present. The coexistence of OSA and COPD (overlap syndrome) is increasingly recognised and can be effectively treated with CPAP.

Persistent problems with LTOT in COPD include poor compliance with therapy by patients, and suboptimal adherence to guidelines by practitioners. Patients may become hypoxaemic during activities of daily living despite LTOT as the flow rate is insufficient or may overuse the therapy resulting in hypercapnia. Autotitrating delivery systems to adjust to variable oxygen requirements are being developed.

Ambulatory oxygen therapy is added to correct hypoxaemia on exercise. In sedentary patients using LTOT, ambulatory oxygen is usually prescribed at the same flow rate as in daytime use. In active and mobile LTOT recipients and patients who desaturate on exertion but do not fulfil criteria for LTOT, optimum flow rates can be derived from a standard 6-min or shuttle walk test, aiming to correct S_{aO_2} to >90%, reduce dyspnoea and increase exercise tolerance. There is no evidence to support the routine use of short-burst oxygen therapy in COPD, but it may be prescribed to palliate symptoms in end-stage disease. The evidence to support the use of short-burst oxygen therapy in advanced cancer is minimal, but it may be helpful in some individuals as part of a comprehensive palliative care plan.

Table 1. Assessment for LTOT

Consider assessment in:
All patients with FEV_1 <30% predicted
Patients with cyanosis
Patients with polycythaemia
Patients with peripheral oedema
Patients with raised jugular venous pressure
Patients with S_{aO_2} on air ≤92%

Table 2. Criteria for LTOT in steady-state patients

Chronic hypoxaemia (P_{aO_2} <7.3 kPa (<55 mmHg) on air)
P_{aO_2} <8.0 kPa (<60 mmHg) on air in addition to pulmonary hypertension, secondary polycythaemia, right heart failure or nocturnal desaturation

Oxygen delivery systems

Oxygen can be delivered by oxygen cylinder, concentrator or liquid oxygen device. LTOT is more cost-effectively delivered in the home by a concentrator. The advantages and disadvantages of the different systems are shown in table 3. LTOT patients should be regularly assessed (at least once a year) to check the suitability of flow rates, adherence to therapy and safety.

Entrainment of oxygen therapy into NIV and CPAP circuits

In patients receiving acute or long-term therapy with NIV or CPAP, additional oxygen therapy may be required to correct S_{aO_2}. Oxygen can be entrained into the circuit *via* a T-piece or through the mask. It is important to note that the more proximal the entrainment (*e.g.* ventilator side of the exhalation port), the greater the inspiratory oxygen fraction (F_{IO_2}) achieved. In addition, F_{IO_2} is likely to be lower than that achieved by delivering a similar oxygen flow rate without NIV/CPAP and is difficult to predict accurately, as increases in inspiratory positive airway pressure may reduce F_{IO_2}.

High-flow nasal cannulae/oxygen therapy

High-flow nasal cannula (HFNC) oxygen therapy was originally developed for use in neonates. It is now widely available for all age groups and comprises a system

Table 3. Comparison of oxygen delivery devices

Delivery system	Advantages	Disadvantages
Compressed oxygen cylinder	Easily available No power required Economical in the short term	Frequent refills required High long-term cost Fire risk
Home concentrator	Permanent source No need for refills Economical in the long term	Power required Needs servicing and spare parts
Liquid oxygen	Small and portable No need for power	Refills required High cost
Portable concentrator	Small and portable No need for refills Can be powered by a car battery	High cost Limited battery life Cannot deliver high flow Pulsed or demand flow, so unsuitable for use during sleep F_{IO_2} during pulsed flow will vary according to pulse duration, trigger sensitivity and oxygen concentration delivered

that delivers a humidified high-flow mixture of oxygen and air at flow rates of up to 40–60 L·min^{-1}, with an F_{IO_2} of 0.21–1.0. The humidification may facilitate secretion mobilisation and the nasal cannula may aid comfort compared to mask interfaces. The high flow generates a low level of positive pressure of around 4 cmH_2O which may help recruit functional residual volume, reduce work of breathing and, together with a dead space flushing effect, improve control of carbon dioxide tension. Trials have suggested better survival rates and more ventilator-free days in acute hypoxaemic patients in the intensive care unit when compared with NIV, and in post-extubation patients HFNC seems better tolerated and noninferior to NIV. HFNC has been used as an adjunct to airway intubation, for example during bronchoscopy. Difficulty in blinding trial arms is a source of bias in most trials.

From a chronic perspective, HFNC therapy has been used on a case-by-case basis for long-term therapy in patients unable to tolerate NIV, or in those with intractable hypoxaemia due to interstitial lung disease. There are no controlled trials in these areas.

Further reading

- British Thoracic Society Working Group on Home Oxygen Services (2006). Clinical component for home oxygen service in England and Wales. London, British Thoracic Society.
- British Thoracic Society (2017). BTS Guideline for oxygen use in healthcare and emergency settings. https://www.brit-thoracic.org.uk/quality-improvement/guidelines/emergency-oxygen/
- Helviz Y, *et al.* (2018). A systematic review of high-flow nasal cannula for adult patients. *Crit Care*; 22: 71.
- Lacasse Y, *et al.* (2018). Home oxygen therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2018; 197: 1254–1264.
- Long-Term Oxygen Treatment Trial Research Group, *et al.* (2016). A randomized trial of long-term oxygen for COPD with moderate desaturation. *N Engl J Med*; 375: 1617–1627.
- Nocturnal Oxygen Therapy Trial Group (1980). Continuous or nocturnal oxygen therapy in hypoxaemic chronic obstructive lung disease, a clinical trial. *Ann Intern Med*; 93: 391–398.
- O'Driscoll BR, *et al.* (2008). British Thoracic Society Guideline for emergency oxygen use in adult patients. *Thorax*; 63: Suppl. 6, vi1–vi68.
- Report of the Medical Research Council Working Party (1981). Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet*; 1: 681–685.
- Thys F, *et al.* (2002). Determinant of F_{I,O_2} with oxygen supplementation during noninvasive two-level positive pressure ventilation. *Eur Respir J*; 19: 653–657.

Smoking-related diseases

Linnea Hedman

Tobacco smoking is the leading preventable cause of premature death and disease. For a long time, smoking has been considered a socially accepted activity when instead it should be regarded as a lethal threat to individual and public health. A threat that is most prominent for the most vulnerable members of society; persons of lower socioeconomic status and educational level and those with mental illness or substance use disorders.

The tobacco epidemic

Before the 20th century, tobacco was usually smoked in pipes, snuffed or chewed. The sale of the manufactured cigarette increased dramatically at the beginning of the 20th century and it has been the dominant form of tobacco use ever since. In most European countries, tobacco consumption peaked in the 1960s. Although harmful effects were suspected as a result of tobacco smoking, major actions into the research of lung and airway diseases did not start until the 1950s. Important publications include the British study by Doll *et al*. (2004) on the causal effect between smoking and lung cancer and the American Surgeon General’s report on smoking and health in 1964.

In the 1960s, the first tobacco control measures included health warnings on packages and public educational programmes. The efforts were further intensified in the 1980s with the evidence that exposure to second-hand smoke was related to death and disease among nonsmokers. Since the beginning of the century, more and more countries have passed laws on smoke-free public places and workplaces. The World Health Organization (WHO) monitors tobacco use and prevention policies through the Framework Convention on Tobacco Control and reports that there have been substantial advances in the adoption of strong tobacco control policies in all regions of the world and among countries of all income levels. Almost two-thirds

Key points

- Tobacco smoking is the leading preventable cause of premature death and disease.
- Tobacco smoking is causally related to diminished overall health, in general, and respiratory and cardiovascular diseases and cancer, in particular.
- Exposure to second-hand smoking is related to disease among nonsmokers.
- Protecting children from exposure to second-hand smoke and the effects of tobacco marketing is of utmost importance.

of the people in the world are now covered by at least one tobacco control measure such as warning labels, advertising bans, taxations, smoke-free environments or mass media campaigns. However, the WHO states that the existing policies have not been enough to end the tobacco epidemic and that much more work remains to be done to protect people from the illness, disability and death caused by tobacco smoke.

Compared with adults, adolescents experience more positive effects when they smoke and those who start to smoke at a younger age develop a stronger dependence, which increases the risk of continued use in adulthood. The window of opportunity for the tobacco industry to recruit new users, or addicts, is mainly open during adolescence. The risk of becoming a smoker during adolescence increases if there are tobacco users in the environment where the adolescents are present: at home, among friends, watching role models on social media, TV and other forms of advertisement. To end the tobacco epidemic, children and future generations must be protected from exposure to tobacco and nicotine products.

Tobacco smoke and nicotine

Tobacco smoke contains a mixture of more than 7000 substances including nicotine, carcinogens, heavy metals, tar and toxicants. Nicotine is the component responsible for causing the addiction and thus sustained exposure to all the harmful substances in a cigarette, which in turn increase the risk for smoking-related diseases. However, nicotine itself may be more harmful than previously known. Although human studies are lacking, experimental studies have proposed that nicotine may play a role in the carcinogenic process. The harmful effects of nicotine are further supported by the fact that nicotine exposure during pregnancy may have adverse effects on fetal health, contributing to preterm delivery, stillbirth and lasting consequences for brain and lung development.

Overall mortality

Tobacco smoking is the leading preventable cause of premature death. Mortality increases with both the number of cigarettes smoked per day and years of smoking. Retrospective observations of trends in high-income countries show an increasing prevalence of smoking followed by an increase of smoking related deaths 30–40 years later. The pattern is similar in men and women; however, the increase in smoking usually occurs 10–20 years later in women. In countries such as Sweden, where the proportion of smokers in the population has been decreasing over the past 30 years, smoking-related deaths, including lung cancer mortality, is declining.

Respiratory symptoms and diseases

Smoking is the major cause of respiratory symptoms such as chronic cough, increased phlegm production, wheezing and dyspnoea, as well as many respiratory diseases such as chronic bronchitis, emphysema and COPD.

COPD is characterised by airflow limitation that is progressive and not fully reversible. The airflow limitation is measured by spirometry and presented as the FEV_1. Smoking contributes to an accelerated decline of FEV_1 beyond what is expected from ageing and, thus, is the most important risk factor for COPD. The most important intervention to slow the lung function decline is smoking cessation. According to the WHO, the global prevalence of COPD is likely to increase due to higher smoking prevalence and ageing populations in many countries. However, following a continuing decrease in smoking over the past two to three decades, a decrease in the prevalence of COPD has been observed in Northern European countries.

There is suggestive evidence of a causal relationship between tobacco smoking and the incidence of asthma in adolescents and adults. Among individuals with asthma there is growing evidence of associations between tobacco smoking and exacerbation of disease, use of emergency healthcare and poor asthma control and quality of life. Moreover, asthmatics who smoke have attenuated response to inhaled and systemic corticosteroids.

Infectious diseases such as TB, acute bronchiolitis, pneumonia, common cold and influenza are more common and severe among smokers than nonsmokers. Interstitial lung diseases such as respiratory bronchiolitis-associated interstitial lung diseases, desquamative interstitial pneumonia and pulmonary Langerhans cell histiocytosis are more likely to develop among smokers.

Second-hand smoking

Smoking affects the health of others through the harmful effects of second-hand smoking. Although the inhaled dose of fine particulate matter is >300-fold higher for a smoker than those exposed to second-hand smoke, the level of emitted particulate matter from second-hand smoke is still high enough to increase the risk for several adverse health effects. Moreover, the level of particulate matter is comparable to outdoor air pollution, for instance from car exhaust. Maternal smoking during pregnancy and exposure to second-hand smoke early in life increase the risk for impaired lung function, respiratory symptoms and asthma, as well as sudden infant death syndrome, middle ear infections and congenital abnormalities such as cleft lip. Moreover, it may have lifelong effects increasing the risk for respiratory symptoms and diseases, stroke, lung cancer and coronary heart disease in adulthood. Furthermore, children whose parents smoke are more likely to become smokers in the future.

Cardiovascular diseases

Tobacco smoking is a major cause of cardiovascular morbidity and mortality. Exposure to second-hand smoking is associated with increased risk for stroke and high blood pressure. Smoking cessation is one of the most effective strategies for both primary and secondary prevention of cardiovascular diseases.

Cancer

There is conclusive evidence that tobacco smoking causes cancer of the lung, as well as throat, stomach, liver, pancreas, kidney, cervix, bladder, colorectal cancer and acute myeloid leukaemia. Among women, there is suggestive evidence of causality between tobacco smoke and breast cancer. Among men, there is evidence suggesting higher risk for death from prostate cancer in smokers than nonsmokers. Smoking is related to shorter survival after a diagnosis of cancer and accounts for one-fifth of all cancer-related deaths, of which lung cancer is the most common. However, a cancer patient who is a current smoker can improve the prognosis by quitting smoking at any time.

Future challenges

In many European countries, the prevalence of smoking has stabilised or declined in past decades. Nevertheless, the consequences of tobacco smoking remain the single largest avoidable health risk. Smoking contributes to inequalities in health as the prevalence of smokers is highest in vulnerable groups such as those with mental illness and lower socioeconomic status. These groups may be less susceptible to prevention efforts, setting heavy demands on how they are designed.

The tobacco industry introduces and markets new products that attract new customers and maintain nicotine addiction in already established users. Both electronic cigarettes and heated tobacco products are portrayed by the tobacco industry as a substitute to conventional cigarettes and as a means of smoking cessation. However, it has become more common that smokers use multiple products. Exposure studies indicate that e-cigarettes may have both respiratory and acute vascular effects; however longitudinal observational studies are still lacking. Still, e-cigarettes and heated tobacco products contain and emit numerous carcinogenic and toxic substances that that have known biological effects in humans. It is too soon to tell if these novel products will contribute to more smokers quitting conventional cigarettes or if they will increase the burden of symptoms and diseases.

Summary

Despite conclusive evidence on the harmful effects of smoking and second-hand smoke being known for decades, there is still much to be done to change public beliefs, attitudes and behaviour. There are interventions, regulations and policies to reduce initiation of tobacco use among children and to encourage quitting among smokers proven to be effective. These measures need to be even more strongly and comprehensively implemented in order to help people to live longer, healthier and more productive lives, free from tobacco. The tobacco epidemic is far from over.

Further reading

- Bray FI, *et al.* (2010). Lung cancer mortality trends in 36 European countries: secular trends and birth cohort patterns by sex and region 1970–2007. *Int J Cancer*; 126: 1454–1466.
- Doll R, *et al.* (2004). Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ*; 328: 1519.
- U.S. Department of Health and Human Services (2014). The health consequences of smoking – 50 years of progress. A report of the Surgeon General, 2014. Atlanta, U.S. Department of Health and Human Services. www.surgeongeneral.gov/library/reports/50-years-of-progress/index.html
- Wipfli H, *et al.* (2016). One hundred years in the making: the global tobacco epidemic. *Annu Rev Public Health*; 37: 149–166.
- World Health Organization (2017). Tobacco-free generations – protecting children from tobacco in the WHO European Region. Copenhagen, WHO Regional Office for Europe.

Treatment of tobacco dependence

Charlotta Pisinger

The epidemic of disease caused by smoking ranks among the greatest public health catastrophes of the last century, and it has been estimated that smoking will kill ~1 billion people in the 21st century. The good news is that most smokers want to quit, and evidence-based tobacco dependence treatments exist, and are safe and very cost-effective. The effect of smoking cessation is very strong, even among individuals aged ≥80 years. Smoking cessation is the cornerstone of treatment of respiratory patients: it slows down the progression of COPD, and increases survival in patients with COPD and patients with early-stage lung cancer.

Why do my respiratory patients continue to smoke?

The proportion of people with COPD who continue to smoke has been estimated to be between 30% and 70%. Many patients know little about the health hazards of smoking, and believe that factors for which the smoker cannot be blamed (*e.g.* bad luck, pollution or heredity) and not smoking is the cause of their disease. Smoking COPD patients are characterised by high nicotine dependence, deep inhalation and having smoked many pack-years (1 pack-year=20 cigarettes smoked in 1 year) during their lifetime. Smoking COPD patients often have little education, low health literacy, and are deprived and/or mentally vulnerable. Most COPD patients experience depression and/or anxiety. All these factors are associated with low quit rates. A growing body of evidence suggests that majority of COPD patients, especially those who report high levels of nicotine dependence, will require intensive smoking cessation support in order to quit.

Smoking is not a 'bad habit' but a chronic dependence disorder with high relapse rates. Cigarettes are highly addictive, similarly to heroin and cocaine. Patients who try to quit will often experience nicotine abstinence symptoms such as anxiety, bad mood/depressive symptoms, difficulties concentrating, restlessness, insomnia,

Key points

- As a minimum, smoking status should be identified, and all smoking patients should be offered brief advice and a prescription for smoking cessation medication, or very brief advice and referral to a trained smoking cessation counsellor/clinic.
- A combination of high-intensity counselling and pharmacotherapy is the most effective strategy for treating tobacco use among patients with COPD.
- Combination nicotine replacement therapy (patch plus *e.g.* inhaler or spray) and varenicline are most effective and equally effective as quitting aids.

frustration and anger. Only approximately 3–5% succeed in stopping smoking when they try to quit ‘cold turkey’ (without help). Tobacco dependence is often physical (caused by nicotine), mental (smokers get used to handling difficult or stressful situations in life by lighting up) and social (quitting smoking can be experienced as a loss of social network). Self-blame, guilt, previous failed attempts to quit and withdrawal symptoms may result in hopelessness. Many COPD smokers believe they are unable to quit but they have the same high wish to quit (~70%) and the same number of previous quit attempts. About every second smoking COPD patient wants assistance to quit.

The reluctant smoker

If the reluctant smoker says ‘no thanks’ to smoking cessation, they should not be left with a feeling of guilt. As tobacco dependence is a chronic disease, smoking should be addressed at every contact with the patient and assistance to quit should be offered repeatedly. A ‘no thanks’ is not a lifelong rejection. Smokers who are unwilling to quit who are offered nicotine-replacement therapy significantly increase their quit rate.

The basics

Much research exists looking into what works for ‘healthy’ smokers. It is still unclear whether smokers with COPD/respiratory disease are different from healthy smokers with regard to which treatments work best to help them stop smoking.

Routine identification of smokers is mandatory. Smoking cessation is recommended for all respiratory patients who smoke, regardless of stage of disease (except terminal patients), and all categories of medical personnel should provide smoking cessation advice for all hospitalised patients. Smoking cessation interventions should take place both in primary care and in specialist settings (high level of evidence), and all health professionals involved in the treatment of COPD should be trained in evidence-based smoking cessation treatment (high level of evidence).

The efficacy of brief advice is highest at a duration of 3–5 min of a doctor’s intervention. Current smokers who are hospitalised should, as a minimum, receive nonjudgmental, brief smoking cessation counselling, prescription of smoking cessation medication, or referral to a specialised smoking cessation counsellor or centre (high level of evidence).

Very Brief Advice: a referral strategy

The Very Brief Advice (VBA) method is the shortest method (30 s, does not require any specific skills; low level of evidence), and a good choice for the doctor who is not a smoking cessation specialist and has very limited time. The doctor must have the option of referral to trained smoking cessation specialists or clinics that will contact the smoker. Smokers not ready to quit can change their mind very quickly and accept an assisted quit attempt without longer contemplation.

- **Ask** Do you (still) smoke?
- **Advise** Many smokers find it difficult to quit. The best way is to get help. Counselling and smoking cessation medication will highly increase your chances of quitting.
- **Act** May I ask a smoking cessation counsellor to contact you after discharge?

A combination of high-intensity behavioural support and medication is best

There is evidence that interventions that combine pharmacotherapy and behavioural support increase smoking cessation success compared to a minimal intervention or usual care. Smokers with COPD who receive a combination of high-intensity behavioural support and medication are more than twice as likely to quit as people who receive behavioural support alone.

In a randomised controlled trial where smoking COPD patients in the intervention group were admitted to hospital for 2 weeks and offered nicotine replacement therapy (NRT), group-based counselling, physical exercise and encouraging phone calls after discharge, 52% were smoke-free compared with 7% in the control group (usual care) after 1 year.

Behavioural support

High-intensity behavioural interventions that begin during a hospital stay and include ≥1 month of supportive contact after discharge promote smoking cessation among hospitalised patients, independent of diagnosis. Providing behavioural support in person or *via* telephone for people using pharmacotherapy to stop smoking has a small but important effect. Increasing the amount of behavioural support is likely to increase the chance of success by about 10–25%. Individual or group-based counselling is equally effective. Repeated counselling (*e.g.* four or five times) is most effective.

Assisting your smoking patient in smoking cessation

The 5As approach (ask, advise, assess, assist and arrange) is recommended (figure 1). To assist a smoker with smoking cessation, the counsellor (health professional or others) needs to assess:

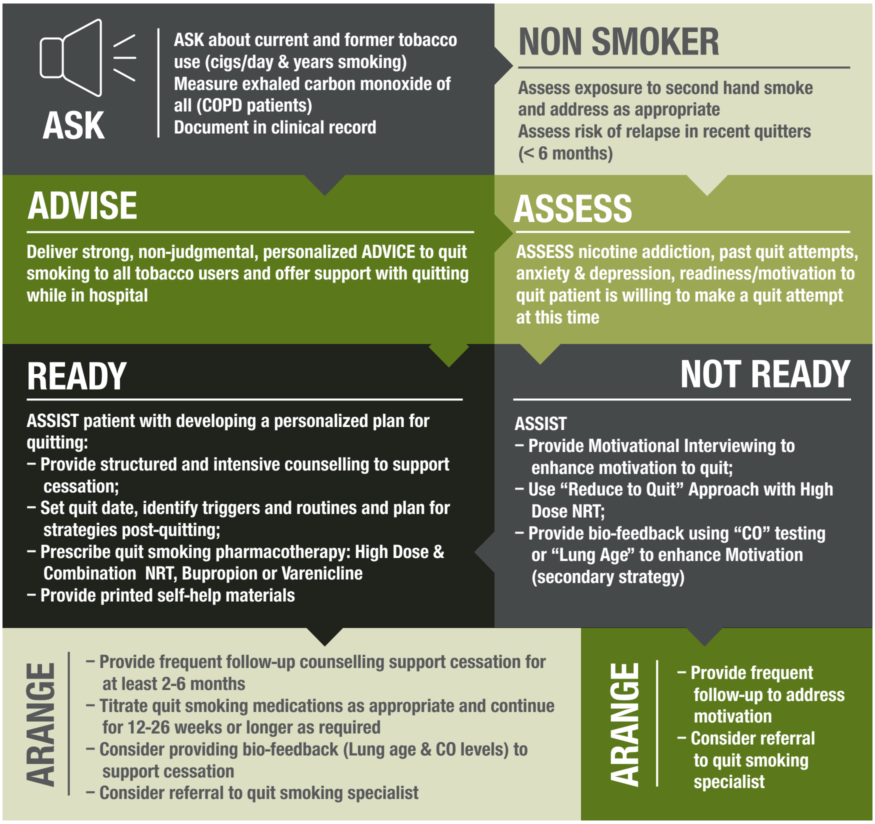
- daily tobacco consumption and duration
- carbon monoxide level (useful)
- analysis of previous quit attempts
- readiness to quit
- tobacco dependence

The Heaviness of Smoking Index is a very simple and quick test to establish how nicotine dependent the patient is. The two questions are: ‘How many cigarettes, on average, do you smoke per day?’ and ‘How soon after waking do you smoke your first cigarette?’ The more cigarettes smoked daily and the sooner the smokers lights the first cigarette after waking, the more nicotine dependent they are. Other, more time-consuming, nicotine dependence scores exist (*e.g.* the Fagerström score).

Motivational interviewing increases 6-month cessation rates by ~30%. Expressing empathy and avoiding arguments (rolling with resistance) is an important tenet of motivational interviewing. To help the patient explore and resolve ambivalence, the clinician may ask the smoker to rate their motivation to quit on a scale from one to 10. This can be followed by the question, ‘Why are you a *x* and not a 10 (or one) on the scale?’

Smoking cessation medication

NRT, bupropion and varenicline have been shown to improve the chances of quitting. Combination NRT (patch and *e.g.* gum, inhaler or spray) and varenicline are equally effective as quitting aids. Nortriptyline and cytisine (routinely used in Eastern Europe) also improve the chances of quitting. None of the treatments appear to have an incidence of adverse events that would mitigate their use.



ASK

ASK about current and former tobacco use (cigs/day & years smoking)
Measure exhaled carbon monoxide of all (COPD patients)
Document in clinical record

NON SMOKER

Assess exposure to second hand smoke and address as appropriate
Assess risk of relapse in recent quitters (< 6 months)

ADVISE

Deliver strong, non-judgmental, personalized ADVICE to quit smoking to all tobacco users and offer support with quitting while in hospital

ASSESS

ASSESS nicotine addiction, past quit attempts, anxiety & depression, readiness/motivation to quit patient is willing to make a quit attempt at this time

READY

ASSIST patient with developing a personalized plan for quitting:
- Provide structured and intensive counselling to support cessation;
- Set quit date, identify triggers and routines and plan for strategies post-quitting;
- Prescribe quit smoking pharmacotherapy: High Dose & Combination NRT, Bupropion or Varenicline
- Provide printed self-help materials

NOT READY

ASSIST
- Provide Motivational Interviewing to enhance motivation to quit;
- Use "Reduce to Quit" Approach with High Dose NRT;
- Provide bio-feedback using "CO" testing or "Lung Age" to enhance Motivation (secondary strategy)

ARANGE

- Provide frequent follow-up counselling support cessation for at least 2-6 months
- Titrate quit smoking medications as appropriate and continue for 12-26 weeks or longer as required
- Consider providing bio-feedback (Lung age & CO levels) to support cessation
- Consider referral to quit smoking specialist

ARANGE

- Provide frequent follow-up to address motivation
- Consider referral to quit smoking specialist

Figure 1. The 5As (ask, advise, assess, assist and arrange). Reproduced from Behrakis et al. *(2017) with permission from the publisher.*

There is lack of evidence for electronic cigarettes or smokeless tobacco as effective smoking cessation tools. In a real-life setting, use seems rather to undermine smoking cessation. The European Respiratory Society does not recommend their use.

Use of spirometry, lung age and carbon monoxide testing

Exhaled air carbon monoxide is a useful noninvasive biomarker of tobacco smoking exposure. There is some evidence that carbon monoxide measurement can be used as a motivational tool to support quit attempts. The role of spirometry and 'lung age' for increasing patient motivation to quit smoking deserves further investigation (low level of evidence).

Dealing with relapse

Most smokers relapse to smoking. The relapse rate is highest in the first weeks of cessation. Long-term follow-up is recommended for ≥6 months to confirm abstinence and to cover the period of highest relapse risk. Extended treatment with varenicline (moderate-certainty evidence) and extended treatment with NRT (low-certainty evidence) helps to prevent relapse. There is no benefit from extended treatment with bupropion (moderate-certainty evidence) in preventing relapse in assisted abstainers. Evidence is inconclusive when it comes to behavioural interventions that teach people to recognise situations that are high risk for relapse along with strategies to cope with them.

Further reading

- Bai JW, *et al.* (2017). Smoking cessation affects the natural history of COPD. *Int J Chron Obstruct Pulmon Dis*; 12: 3323–3328.
- Behrakis PK, *et al.* (2017). Tobacco cessation guidelines for high-risk populations (TOB.g). http://tob-g.eu/wp-content/uploads/TOB-G-BOOK-DIGITAL-VERSION.pdf
- Cahill K, *et al.* (2013). Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev*; 5: CD009329.
- European Network for Smoking and Tobacco Prevention (2012). ENSP Guidelines for Treating Tobacco Dependence. Brussels, ENSP.
- Lai DT, *et al.* (2010). Motivational interviewing for smoking cessation. *Cochrane Database Syst Rev*; 1: CD006936.
- Livingstone-Banks J, *et al.* (2019). Relapse prevention interventions for smoking cessation. *Cochrane Database Syst Rev*; 2: CD003999.
- Pisinger C (2019). ERS Position Paper on Tobacco Harm Reduction. A statement by the ERS Tobacco Control Committee. www.ersnet.org/advocacy/eu-affairs/ers-position-paper-on-tobacco-harm-reduction-2019
- Rigotti NA, *et al.* (2012). Interventions for smoking cessation in hospitalised patients. *Cochrane Database Syst Rev*; 5: CD001837.
- Stead LF, *et al.* (2012). Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev*; 10: CD008286.
- Stead LF, *et al.* (2016). Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev*; 3: CD008286.
- Sundblad BM, *et al.* (2008). High rate of smoking abstinence in COPD patients: smoking cessation by hospitalization. *Nicotine Tob Res*; 10: 883–890.
- van Eerd EA, *et al.* (2016). Smoking cessation for people with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*; 8: CD010744.

Long-term ventilation

Anita K. Simonds

Long-term ventilation (LTV) is a term usually used to describe individuals using either NIV or tracheostomy-delivered ventilation daily for >3 months in the user's home or a long-term care facility. Lloyd-Owen *et al.* (2005) showed a widespread variation in prevalence of LTV provision in Europe. Numbers have grown considerably since 2005 but these data exclude OSA patients using CPAP. There was also a north–south divide with more neuromuscular and chest wall patients receiving LTV in northern Europe, and more chronic lung disease patients using LTV in southern Europe. As the prevalence of these conditions does not vary substantially, differences in the pattern of LTV are likely to be historical rather than evidence based.

Pathophysiology

Chronic ventilatory decompensation occurs when the load placed on the respiratory system outstrips its capacity. This occurs in restrictive disorders, such as chest wall and neuromuscular disease, and in chronic lung diseases, such as COPD, CF and bronchiectasis. Disorders of ventilatory drive are less common but LTV is required in patients with congenital central hypoventilation syndrome (CCHS) or other, acquired causes of failure of ventilatory drive, such as brain stem cerebrovascular or cervical spinal cord injury events. The clinical course in many patients is punctuated by episodes of acute-on-chronic ventilatory failure precipitated by chest infections (*e.g.* COPD and CF). In others, there is a clear-cut vicious cycle of decline. For example, in chest wall or neuromuscular disease, small lung volumes lead to initially nocturnal hypoventilation and, ultimately, diurnal ventilatory failure if sleep disordered breathing is not addressed.

Key points

- Long-term ventilation (LTV) is defined by the requirement for daily ventilatory support for >3 months.
- The majority of LTV recipients use NIV *via* pressure pre-set ventilators.
- NIV should be started for symptomatic nocturnal hypoventilation or daytime hypercapnia in restrictive disorders.
- NIV extends survival in motor neurone disease/amyotrophic lateral sclerosis patients and may improve health-related quality of life.
- NIV is most effective in COPD patients with chronic hypercapnia or persistent hypercapnia for >2 weeks after an acute exacerbation, and reduces mortality and readmissions.

Types of LTV

The greatest growth in LTV over the last two decades has been in the use of home NIV. This is virtually all mask ventilation or *via* an oral/nasal interface, as very few patients receive domiciliary negative pressure ventilation (*e.g. via* cuirass or iron lung). The potential indications for tracheostomy ventilation are bulbar weakness leading to aspiration, near 24-h ventilator dependence, upper airway lesions, difficulties with NIV, neonatal age range and patient preference, although many patients with daytime and nocturnal ventilator dependence can be managed on NIV.

Ventilators

The survey of LTV in Europe (Lloyd-Owen *et al.*, 2005) showed nearly all patients were using positive pressure ventilators (mostly in pressure support mode) with <1% using volume ventilators. Dual-mode ventilators are obtainable but, perhaps not surprisingly, volume ventilators were most commonly used in neuromuscular and chest wall patients, and least frequently used in those with lung disease (COPD/bronchiectasis). Volume-assured ventilation modes, *i.e.* pressure support with pre-specified V'_E, have been developed but only seem to offer advantages in limited situations. Adaptive servoventilation (ASV) has been shown to increase mortality in HF patients with central sleep apnoea and with a left ventricular ejection fraction of <45%, so should not be used in this group. The role of ASV in HF patients with central sleep apnoea (CSA) and less severe heart failure, and those with combined OSA and CSA, or with complex sleep disordered breathing is under investigation.

The choice of ventilatory mode and settings should match the underlying pathophysiology and be carefully titrated to the patient. Further considerations include the age and size of the patient, degree of ventilator dependency, and need for oxygen therapy. Humidification is required for nearly all tracheostomy patients and is indicated in some patients using long-term NIV (*e.g.* those with recurrent or viscid secretions).

The ventilator care plan should adapt to the patient, as patients with progressive disorders will become more ventilator dependent over time and require ventilatory support during the day, and/or progress from NIV to tracheostomy ventilation if bulbar function worsens; and in children, total ventilatory requirements will change with growth. Continued monitoring is vital to reassess ventilatory needs, and this may be facilitated by a range of methods including sleep studies, ventilator data downloads, smart cards and telemonitoring.

Interfaces

Interface choice and comfort are crucial to the success of NIV. Improvements in mask design and materials, including a greater availability of interfaces for adults and children, has assisted the wider uptake of NIV. Mask leak reduces the efficacy of NIV and leads to poor tolerance. Data on leak and delivered volumes can be easily obtained from ventilator downloads and/or telemonitoring.

Tracheostomy

The choice of tracheostomy tube or cannula is dictated by:

- Need for mechanical ventilation
- Ability of the patient to defend the lower airway (adequate cough and bulbar function)

- Temporary or permanent placement
- Neck size and anatomy of the patient

The aim is to protect the airway and optimise ventilation while preserving speech and swallowing function, and minimising complications related to the tracheostomy tube such as sputum plugging, tracheal stenosis and pressure necrosis resulting in haemorrhage. Cuffed tracheostomy tubes may reduce aspiration risk in adults but cuff pressure should be monitored so that it does not exceed 25 mmHg. In any patient with a long-term tracheostomy, correct size and placement, and regular inspection and bronchoscopy are recommended as follow-up. In the last decade, the combination of NIV, cough assist devices such as mechanical insufflation–exsufflation, and enteral feeding has reduced the need for tracheostomy ventilation especially in neuromuscular patient groups.

Chest wall disorders

This group includes patients with scoliosis, old TB lung disease, thoracoplasty and chest wall fibrosis. Patients with scoliosis at high risk of ventilatory decompensation are shown in table 1.

Neuromuscular disease

Neuromuscular disorders can be grouped into those in which the underlying condition is relatively static (*e.g.* previous poliomyelitis and phrenic nerve injury due to brachial neuralgia), those that are slowly progressive (*e.g.* Duchenne muscular dystrophy (DMD) and other myopathies) and those that are rapidly progressive (*e.g.* motor neurone disease (MND)/amyotrophic lateral sclerosis (ALS)). Management plans should therefore take into account the natural history of the condition as well as current ventilator needs.

Most neuromuscular patients have normal lungs apart from occasional atelectasis, so they are relatively easy to ventilate with low pressures; back-up rates are usually required due to profound hypoventilation during REM (rapid eye movement) sleep. Careful consideration of the interface is required as individuals may not be able to affix a mask easily due to weak muscles of the upper limb, and midfacial hypoplasia may occur in children and young patients who start NIV before facial skeletal growth is complete. Near-100% 5-year survival has been reported in previous polio patients receiving NIV. In DMD patients, the use of NIV has extended median survival from 18 to 29 years (Eagle *et al.*, 2002), and many young males with DMD are now surviving into their 30s and 40s.

In severe conditions such as type 1 spinal muscular atrophy (SMA), where survival is poor, NIV may be used with the goal of palliating symptoms and allowing home

Table 1. Risk factors for ventilatory decompensation in scoliosis

Congenital or early-onset scoliosis
Thoracic curve >100°
Curve involves high thoracic and cervical vertebrae
Paralytic aetiology (*e.g.* due to neuromuscular weakness)
Vital capacity <50% predicted
Comorbidity (*e.g.* COPD or morbid obesity)

discharge rather than extending life expectancy. Newer treatments in type 1 SMA, such as nusinersen, may however extend survival, and improve motor function in this group and in older affected children with type 2 SMA.

Bourke *et al*. (2006) showed in a randomised trial of NIV in MND/ALS that overall survival increased by ~7 months. This improvement was predominantly seen in patients with mild-to-moderate bulbar weakness and quality of life improvements were mainly seen in this group too. However, sleep-related symptoms improved, even in patients with severe bulbar disease. Although it is often reported that NIV cannot be used in MND patients with severe bulbar disease, this belief is overplayed, and a trial is recommended in all MND patients who wish to try NIV. Tracheostomy ventilation may be the only solution to aspiration pneumonia but in some bulbar patients, the combination of NIV, a cough assist device and percutaneous gastrostomy feeding works as effectively.

Ventilatory support should be initiated in patients once symptomatic nocturnal hypoventilation is identified, or in the presence of orthopnoea or FVC <80% with symptoms. NIV use may also facilitate physiotherapy.

Spinal cord injury

Individuals with high spinal cord injury or bulbar lesions with no independent ventilatory capacity and an inability to clear secretions will usually require tracheostomy ventilation, but a proportion of quadriplegic patients with minimal ventilatory reserve may be managed by a combination of NIV and cough assist devices. As in other neuromuscular conditions, some patients may be able to augment spontaneous vital capacity by glossopharyngeal 'frog' breathing. Phrenic nerve pacing has a limited role in high spinal cord injury patients and central hypoventilation syndromes, but often requires supplementation with other forms of ventilatory support and can only be effective if phrenic nerve integrity is maintained.

Central hypoventilation syndromes

CCHS affects approximately one in 200000 and is due to mutations in the *PHOX2B* gene. More severe cases experience life-threatening episodes of apnoea or hypoventilation in the first months of life, complicated by other features of autonomic dysregulation such as cardiac arrhythmias or Hirschsprung's disease. In early infancy, use of ventilation *via* tracheostomy is recommended to optimise oxygenation and cognitive function. Transition to NIV may be possible later in childhood. Diaphragm pacing has been used in some CCHS children but often has to be combined with invasive ventilation or NIV. Other genetic syndromes associated with hypoventilation include Arnold–Chiari malformation and inborn errors of metabolism such as pyruvate dehydrogenase deficiency.

The obesity hypoventilation syndrome (OHS) is a form of acquired hypoventilation and is defined by daytime $P_{\mathrm{aCO_2}}$ >45 mm Hg (6.0 kPa) in the presence of a BMI >30 $\mathrm{kg \cdot m^{-2}}$ (in the absence of other causes of ventilatory decompensation). Obesity hypoventilation patients with mild hypercapnia, with or without OSA, may be successfully managed with CPAP therapy. A recent randomised trial of CPAP *versus* bilevel NIV in newly diagnosed OHS patients with a mean carbon dioxide tension of 60 mmHg (8.0 kPa) showed both modes to be equally effective in controlling ventilatory failure, health-related quality of life and adherence at 3 months. More marked hypercapnia, acute acidotic ventilatory decompensation or failure to control sleep disordered breathing with CPAP are indications for nocturnal NIV. In view of the obesity epidemic, OHS patients comprise one of the most rapidly growing groups receiving home NIV. Ventilatory support should be combined with a comprehensive weight loss and exercise programme in these patients, including consideration of bariatric surgery where other weight loss measures have failed. NIV may not reduce cardiovascular risk factors and vascular disease in these individuals, which should be closely monitored and treated.

Chronic obstructive pulmonary disease

Although numerous selected series of hypercapnic COPD patients have shown physiological advantages of LTV, there has been a dearth of adequately powered randomised controlled trials until recently. McEvoy *et al.* (2009) randomised 144 COPD patients with $\mathrm{FEV_1}$ <1.5 L or <50% predicted and stable $P_{\mathrm{aCO_2}}$ >45 mmHg to receive NIV plus long-term oxygen therapy (LTOT) or LTOT alone. The NIV group had an improvement in survival using an adjusted Cox model but there were no gains in quality of life. Subsequently, Kohnlein *et al*. (2014) demonstrated improvement in mortality and $\mathrm{CO_2}$ tension control in stable COPD patients with chronic hypercapnia, whereas Struik *et al*. (2014) showed no difference in mortality or hospitalisation in those COPD patients who were discharged home on NIV immediately after an acute hypercapnic exacerbation, compared to those without domiciliary NIV. More recently, the situation has been clarified by the HOT-HMV trial, which randomised COPD patients to home NIV plus $\mathrm{O_2}$ therapy or $\mathrm{O_2}$ therapy alone if they remained hypercapnic >2 weeks after discharge following an acute exacerbation (Murphy *et al*. 2017). The NIV plus $\mathrm{O_2}$ group showed a significant reduction in 12-month risk of readmission or death (63.4% in NIV+$\mathrm{O_2}$ *versus* 80.4% in those on $\mathrm{O_2}$ alone). These combined results would suggest that this relatively unstable group of COPD patients who remain persistently hypercapnic are those most likely to benefit from home NIV in the long term.

There is a debate on the use of a high-intensity ventilatory approach in COPD patients (high pressure and controlled ventilation). This has been shown to reduce hypercapnia and improve exercise ability but may be less easy to tolerate than lower pressures for some patients. The most important aim is to control nocturnal hypoventilation and as this does not necessarily require high inspiratory pressures or controlled ventilation, ventilator settings should be established on an individual basis.

CF and bronchiectasis

Nocturnal NIV can reduce symptoms, including breathlessness, and improve nocturnal oxygenation, sleep quality, peak exercise level and quality of life in chronically hypercapnic adult patients with CF. Fauroux *et al.* (2008) has also shown stabilisation of lung function in younger CF patients treated for 1 year with nocturnal NIV. Use during physiotherapy can also prove beneficial. Effects on survival are less clear, other than in the situation where NIV is used to ‘bridge’ patients to transplantation.

Case–control studies of patients with bronchiectasis show improvements in oxygenation compared to LTOT alone and, in some groups, the frequency of infective exacerbations may be reduced. Both CF and idiopathic bronchiectasis patients experience ventilation/perfusion mismatch and diffusion problems, and so are likely to require a combination of NIV and LTOT, judged by overnight monitoring of $S_{\mathrm{aO_2}}$ and $P_{\mathrm{aCO_2}}$. To ascertain which patients with CF and bronchiectasis are likely to benefit, a short trial of NIV (*e.g.* for 3 months) may be helpful. Careful attention to physiotherapy and secretion clearance remains vital.

Table 2. Discharge planning considerations for home ventilator patients

Stability and motivation of patient
Competency training of patient, family and carers
Arrangements for servicing and emergency back-up of ventilator equipment, including suction machines, cough assist devices and oxygen concentrator if required
Supply of disposables (*e.g.* masks, suction catheters, ventilator circuits and filters)
Liaison with all members of care team (home and hospital)
Follow-up assessments/appointments planned
Written guides to management of common problems (*e.g.* chest infection)
Suitable modifications to home environment
Risk management plan (*e.g.* battery packs to cover power failure, smaller size tracheostomy tube if difficulties with tube replacement, low and high pressure and disconnection alarms)
Anticipatory care plan detailing agreed actions in event of chest infection, hospital admission, and preferences regarding resuscitation status and intensive care unit admission

Interstitial lung disease

The development of chronic hypercapnia is an end-stage phenomenon in interstitial lung disease (ILD). NIV has been used in clinical series to reduce symptomatic hypoventilation but can be poorly tolerated and there may be a risk of barotrauma. It can therefore be considered in occasional patients, particularly those with intractable symptoms related to hypercapnia, although there is no evidence for this. However, as oxygenation is the main problem, increasing ventilation is unlikely to address this alone (although may facilitate an increase in oxygen flow rate). High-flow nasal cannula therapy is being increasingly used on an individual basis during acute exacerbations of ILD or for palliative purposes, but the evidence base for this is limited.

Discharge planning and follow-up

Planning for discharge in patients receiving tracheostomy ventilation is necessarily more complex than in those using NIV. The key components of a successful discharge plan are listed in table 2.

Further reading

- Bourke SC, *et al.* (2006). Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *Lancet Neurol*; 5: 140–147.
- Eagle M, *et al.* (2002). Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. *Neuromusc Disord*; 12: 926–969.
- Fauroux B, *et al.* (2008). Long-term non-invasive ventilation in patients with cystic fibrosis. *Respiration*; 72: 168–174.
- Howard ME, *et al.* (2017). A randomised controlled trial of CPAP *versus* non-invasive ventilation for initial treatment of obesity hypoventilation syndrome. *Thorax*; 72: 437–444.

- Kohnlein T, *et al.* (2014). Noninvasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med*; 2: 698–705.
- Lloyd-Owen SJ, *et al.* (2005). Patterns of home mechanical use in Europe: results from the Eurovent survey. *Eur Respir J*; 25: 1025–1031.
- McEvoy RD, *et al.* (2009). Nocturnal non-invasive ventilation in stable COPD: a randomised controlled trial. *Thorax*; 64: 561–566.
- Murphy PB, *et al.* (2017). Effect of home noninvasive ventilation with oxygen therapy vs oxygen alone on hospital readmission or death: a randomized tral. *JAMA*; 317: 2177–2186.
- Pepin J-L, *et al.* (2016). Prevention and care of respiratory failure in obese patients. *Lancet Respir Med*; 4: 407–418.
- Simonds AK, ed. (2015). ERS Practical Handbook of Noninvasive Ventilation. Sheffield, European Respiratory Society.
- Struik FM, *et al.* (2014). Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. *Thorax*; 69: 826–834.
- Windisch W, *et al.* (2005). Outcome of patients with stable COPD receiving controlled non-invasive positive pressure ventilation aimed at maximal reduction of P_{aCO_2}. *Chest*; 128: 657–662.
- Young AC, *et al.* (2008). Randomised placebo controlled trial of non-invasive ventilation for hypercapnia in cystic fibrosis. *Thorax*; 63: 72–77.

Pleural infection and lung abscess

Amelia Clive, William Falconer, Clare Hooper and Nick Maskell

Pleural infection

Pleural infection occurs when microorganisms enter the pleural space. It is confirmed when pleural fluid has a positive Gram stain or culture, is frankly purulent or, in the context of sepsis, has an acidic pH (table 1). It is a common and serious medical problem with a rising incidence despite advances in medical management, and has a high mortality rate, particularly in the elderly.

Patients may present with symptoms of fever, cough, sweats and chest pain, although in the elderly, the symptoms may be nonspecific (*e.g.* fatigue and general decline).

Epidemiology

- Pleural infection is most common in the elderly and children but can occur at any age.
- It is twice as common in males.
- Up to 20% of adults with pleural infection have diabetes mellitus.
- Other important risk factors include aspiration, immunosuppression, poor dentition, alcohol abuse, pleural procedures, thoracic surgery and penetrating chest trauma.

Pathophysiology

Sterile, simple parapneumonic effusions are present in around half of community-acquired pneumonia cases. Around 10% of these develop into complex parapneumonic effusions due bacterial migration into the effusion. Pleural infection can also occur

Key points

- Pleural infection is common and serious, with a substantial mortality rate.
- Blood, in addition to pleural fluid, should always be cultured. A higher microbiological yield is achieved if pleural fluid is sent in both a universal container and blood culture bottles.
- Initial management is with broad-spectrum antibiotics and prompt chest drainage.
- Lung abscess has a 10% mortality rate.
- Invasive procedures are only required when a lung abscess does not respond to prolonged empirical antibiotics or an underlying neoplasm is suspected.

Table 1. Clinical classification of pleural infection

	Simple parapneumonic effusion	Complex parapneumonic effusion	Empyema
Pleural fluid appearance	Straw coloured or bloody	Straw coloured, bloody or turbid	Frank pus
Pleural fluid pH	>7.2	Usually <7.2	Should not be measured
Pleural fluid Gram stain	Negative	May be positive	May be positive
Pleural fluid culture	Negative	May be positive	May be positive
Thoracic ultrasound appearance	Usually anechoic No pleural thickening	May show variable echogenicity, septations or loculations	Often homogenously echogenic Usually evidence of pleural thickening Loculations and septations may be present
Immediate management	Effusion usually resolves with antibiotics for pneumonia alone Chest tube drainage can be performed if required for symptomatic relief of breathlessness	Intravenous antibiotics and chest tube drainage	Intravenous antibiotics and chest tube drainage

in the context of hospital-acquired or aspiration pneumonia with effusion. Primary pleural infection, without underlying lung consolidation, is increasingly recognised. It can occur following traumatic or iatrogenic pleural penetration, oesophageal rupture, oropharyngeal or sub-diaphragmatic translocation of bacteria or haematogenous spread.

Bacteriology

Culture positivity rates from pleural fluid can be poor, with the largest series identifying an organism in 40–60% of cases. The microbiology of community-acquired pleural infection and hospital-acquired pleural infection are different, and hence require different empirical antibiotic regimes (table 2). The microbiology of community-acquired pneumonia and that of pleural infection also differ, probably reflecting the more hypoxic environment and lower pH in the pleural cavity compared to the lung, making certain organisms (*e.g.* anaerobes) more pathogenic.

Investigations

If the fluid is accessible, a diagnostic pleural aspiration should be performed to establish the presence of pleural infection in patients who present with sepsis and chest radiographic signs of pleural effusion.

Table 2. Microbiology of pleural infection and empirical antibiotic choices

	Community-acquired pleural infection	Hospital-acquired pleural infection
Microbiology		
Common organisms	*Streptococcus* spp. *Streptococcus anginosus* group *Streptococcus pneumoniae* Anaerobic organisms *Staphylococcus* spp. Gram-negative organisms	*Staphylococcus* spp. MRSA MSSA Gram-negative organisms Enterobacteriaceae *Streptococcus* spp. *Enterococcus* spp. Anaerobic organisms
Rare organisms	*Mycoplasma pneumoniae* *Legionella* *Nocardia* Atypical mycobacteria Fungi Parasites (*e.g. Entamoeba histolytica*)	
Antibiotic choice		
Empirical antibiotic	Penicillin combined with β-lactamase inhibitor	Gram-negative, Gram-positive (including MRSA) and anaerobic cover (higher risk of antibiotic resistance)
Antibiotic example	Amoxicillin+metronidazole	Carbapenem+vancomycin

MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-sensitive *S. aureus*.

Pleural fluid should always be sent for biochemistry (including glucose), culture and cytological examination. If the fluid is nonpurulent, the pH should be obtained using a blood gas analyser (other measurement methods are less accurate). Culturing pleural fluid in blood culture bottles as well as standard containers has been shown to improve the microbiological yield. Additionally, blood cultures may help obtain a microbiological diagnosis in some cases.

In the correct clinical context, features suggesting that a parapneumonic effusion is complex and, hence, requires chest tube drainage include:

- a pleural fluid pH of <7.2 (or pleural fluid glucose of $<2.2\ \text{mmol}\cdot\text{L}^{-1}$), although *Proteus* infection is associated with high pH due to ammonia production
- positive pleural fluid culture or Gram stain
- purulent pleural fluid
- loculation or septation on thoracic ultrasound

Imaging

Chest radiography often demonstrates a pleural effusion and consolidation. When pleural fluid has entered the organising phase, there may be a lentiform pleural opacity (figure 1).

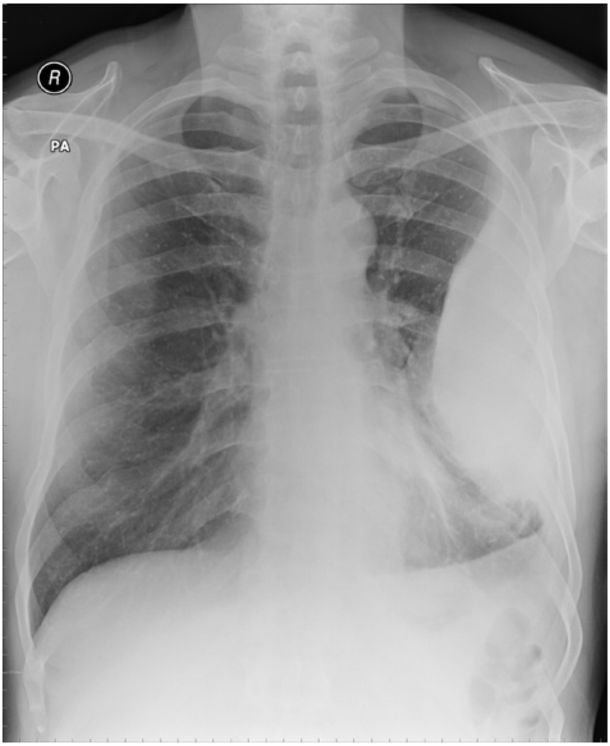


Figure 1. Chest radiograph of left empyema demonstrating a D-shaped, lentiform pleural opacity.

Thoracic ultrasound can help differentiate simple parapneumonic effusions from empyema by the presence of septations and loculations, and/or the presence of echogenic fluid with hyperechoic shadows within it. Ultrasound guidance should always be used to identify a safe site for fluid drainage. It also has a role in monitoring the degree of residual pleural fluid collection after a chest tube is placed.

On contrast-enhanced CT, empyema appears lenticular, well defined and thin walled. It often has an obtuse angle with the chest wall and causes compression of the underlying lung with vascular crowding. In empyema, there is also often bright pleural enhancement with hypertrophy of the extrapleural fat. CT may be required when initial drainage of fluid is incomplete, for the planning of further drains or thoracic surgical intervention, or if other pathology such as pulmonary abscess, neoplastic lesions or oesophageal rupture is suspected.

Management

The following steps should be implemented immediately:

- Broad-spectrum intravenous antibiotics
- Chest tube drainage
- Nutritional supplementation (oral or nasogastric)
- Thromboprophylaxis
- Vigilant monitoring for evidence of worsening sepsis indicating need for early thoracic surgery

Antibiotic choice is usually governed by local prescribing policies, and should include antibiotics with broad-spectrum coverage and good penetration to the pleural space (table 2). When cultures are available, antibiotics should be modified accordingly. As anaerobes are difficult to culture and often co-exist with aerobic organisms, their presence should be assumed and cover continued, unless *Streptococcus pneumoniae* is isolated as this is not known to co-exist with anaerobes. The total duration of antibiotic course and the timing of the *i.v.* to oral switch depends on clinical response, bacteriology, radiology and inflammatory markers. Generally, experts advocate a total of ≥4 weeks of antibiotics but this has not been evaluated in clinical trials.

In a clinically stable patient with a small empyema, chest tube drainage may be impractical and, hence, treatment with prolonged antibiotics and careful follow-up may suffice. However, in the majority of cases, drainage of the fluid is advocated. Small-bore (12–14 French) chest tubes are generally preferred to large-bore tubes as they can be placed *via* a Seldinger technique, are more comfortable and there is no evidence to suggest fluid drainage is compromised. Regular saline flushes (20 mL 6-hourly) help to maintain tube patency and larger-volume 0.9% saline irrigation of the pleural space has been adopted by some European centres, with reports of improved primary treatment success rates. Observational studies report success using local anaesthetic thoracoscopy for initial management, although clinical trial data to support its use are awaited with interest.

The viscosity of the pleural fluid and degree of septation may impair tube drainage. A randomised trial evaluating the combination of intrapleural tissue plasminogen activator (tPA) and DNase demonstrated improved radiological outcomes and trends towards a reduction in need for surgery and duration of hospital stay. This treatment strategy is increasingly used in those unfit for surgery or during initial medical management to maximise fluid drainage and is generally well tolerated. Observational, multicentre data have shown 92% of those who received tPA/DNase avoided surgical intervention.

~15% of patients will ultimately require surgical intervention for empyema, predominantly due to failure of sepsis to improve despite initial appropriate medical treatment with antibiotics and tube drainage. Whilst surgical and anaesthetic complications are more common in the elderly and frail, these patients have the highest mortality and, hence, early surgical referral for a limited surgical drainage procedure may be indicated in this group. Some European centres advocate early thoracoscopy in pleural infection but randomised data demonstrating benefit are lacking.

Available surgical approaches include:

- Video-assisted thoracoscopic surgery (VATS)
- Open thoracotomy and decortication
- Rib resection and open drainage (often performed under local anaesthetic)
- Mini-thoracotomy (usually VATS-assisted)
- Local anaesthetic thoracoscopy

Prognostication

The prognosis of pleural infection can vary widely but mean mortality rates are reported to be ~15%. The elderly and those with hospital-acquired infection have higher mortality.

The RAPID score has been developed to identify those who are at the highest risk of a poor outcome. It scores patients based on their urea, age, fluid purulence, infection source (community or hospital acquired) and albumin resulting in an overall low, medium or high RAPID score, which reflects mortality at 3 months (1.5%, 17.8% and 44.7%, respectively, from external validation data). Its clinical utility in guiding clinical management (*e.g.* expediting early surgery in high-risk patients) needs further evaluation in trials.

Patients should be followed up for ≥3 months to allow the early detection of recurrent sepsis or persistent breathlessness.

Indwelling pleural catheter-related pleural infection

Incidence of indwelling pleural catheter (IPC)-related pleural infection is ~4% and the diagnosis is similar to patients without an IPC. However, potential diagnostic pitfalls include a low pleural pH or elevated pleural lactate dehydrogenase as a result of the underlying malignancy (rather than infection), or a positive pleural fluid culture as a result of colonisation of the IPC without genuine pleural infection. It is therefore important to consider the patients symptoms, blood parameters and fluid appearance in this context when making a diagnosis of IPC-related pleural infection.

There are data that IPC-related pleural infection can be effectively treated with antibiotics and drainage of the collection using the IPC. Initial removal of the IPC is therefore rarely required. However, *i.v.* antibiotics and a period of free drainage from the IPC may be necessary in the initial stages. The tPA/DNase regime may be given *via* the IPC if required.

Lung abscess

Lung abscesses are caused when an area of infected lung becomes necrotic, which results in the development of a cavity within the lung itself. In contrast to pleural infection, the incidence and mortality rate of lung abscess have steadily declined since the advent of penicillin.

Risk factors include:

- Male sex (2/1 ratio)
- Immunocompromised states
- Aspiration due to any cause
- Poor dental hygiene and tooth extraction
- Pneumonia (particularly *Staphylococcus aureus* and *Klebsiella pneumoniae*).
- Bronchial obstruction (*e.g.* endobronchial neoplasm is present in 10–20% cases)
- Haematogenous spread of infection secondary to septic embolisation (*e.g.* tricuspid valve endocarditis and Lemierre’s syndrome; acute oropharyngeal infection caused by *Fusobacterium* spp. results in jugular vein thrombophlebitis and metastatic septic embolisation to the lung)

Diagnosis

Symptoms may be acute or insidious in onset and commonly include cough (often productive of purulent or blood-stained sputum, caused by the abscess eroding into an airway), fever, chest pain, night sweats and weight loss. There may be no specific examination findings or chest auscultation may mimic pneumonia. Anaemia is common and inflammatory markers are likely to be raised.

Imaging

Plain chest radiography classically demonstrates a well-circumscribed, thick-walled opacity, which may contain an air–fluid level. Right-sided abscesses are twice as common as left. Dependent segments are most commonly affected when the abscess is caused by aspiration of gastric contents. Multilobar involvement with multiple abscesses suggests an extrapulmonary source of infection *via* haematogenous spread.

CT is usually required to distinguish a parenchymal abscess from empyema and may assist in the detection of neoplastic lesions. Abscesses often have an irregular, thick wall, have an indistinct outer margin that makes an acute angle with the chest wall, and the surrounding lung usually appears normal (figure 2).

The radiological appearances of a lung abscess may be mimicked by other pathologies, including:

- Neoplastic lesions
- Pulmonary vasculitis
- Pulmonary infarction
- Bullae and cysts
- Rheumatoid nodules
- Pneumoconiosis
- Mycobacterial infection

Bacteriology and obtaining cultures

The microbiology of lung abscesses has changed over recent decades due to an increase in immunocompromise and immunosuppression. In >50% of cases, lung abscesses are polymicrobial.

Anaerobes (*e.g. Fusobacterium*, *Prevotella* and *Peptostreptococcus* spp.), often originating from the oropharynx, are present in 30–50% of cases and may be particularly important in the context of aspiration. However, aerobic bacteria are more commonly identified (particularly *K. pneumoniae* and *S. aureus*). Fungi, *Nocardia*, mycobacteria, *Amoeba*, actinomycetes and *Echinococcus* are more unusual causes of a parenchymal lung abscess, particularly in the immunocompromised.

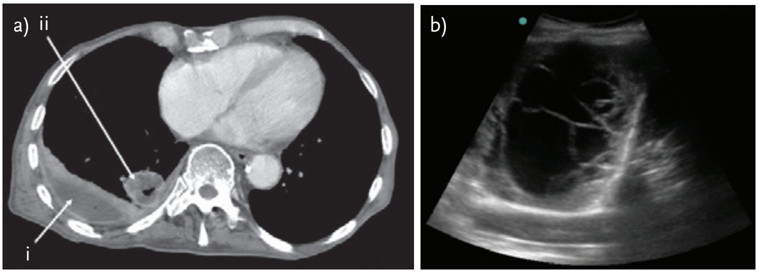


Figure 2. a) CT image of i) right pleural empyema and ii) cavitating pulmonary abscess (arrowhead). b) Ultrasound image of pleural empyema.

Most patients are treated effectively with broad-spectrum antibiotics in the absence of a microbiological diagnosis; however, sputum and blood should be cultured. Sputum is of limited value in the detection of anaerobic organisms due to the frequent contamination with normal upper respiratory tract flora but can be useful to identify aerobic organisms.

Bronchoscopy is not routinely required and bronchial washing cultures often fail to narrow antibiotic selection beyond empirical choices. However, bronchoscopy is indicated when there is suspicion of underlying endobronchial neoplasm, inhaled foreign body, poor response to initial treatment or suspicion of unusual pathogens (*e.g.* fungi or mycobacteria).

Image-guided percutaneous aspiration using CT, ultrasound or fluoroscopy obtains a microbiological diagnosis in 80–90% of cases and changes antibiotic choice in up to 47%. Due to a relatively high risk of pneumothorax (~14%) as a complication of these techniques, it is usually reserved for cases that do not respond to empirical broad-spectrum antibiotics.

Management

A prolonged course of appropriate antibiotics is the foundation of successful treatment, the duration of which depends on clinical and radiological response. β-lactam/β-lactamase inhibitor combinations cover the majority of causative bacteria, but local antibiotic policies should guide antibiotic selection.

Chest physiotherapy plays an important role and postural drainage may help to clear secretions from the abscess itself. Patients with very large abscesses should ideally be placed in the lateral decubitus position with the abscess side down to prevent spread of the infection to the contralateral lung and respiratory compromise should the abscess suddenly discharge its contents into the airway. Preventative measures to avoid further aspiration of gastric contents are also important.

Fever and infective symptoms usually settle within a week of appropriate antibiotics. Failure to improve should raise the suspicion of drug-resistant organisms, such as methicillin-resistant *S. aureus* (particularly in the case of hospital-acquired infection), or other pathologies, such as TB or malignancy. Sustained resolution of sepsis is the most important marker of successful conservative management as radiological resolution can take up to 3 months.

When appropriate antibiotic therapy fails (in 11–21% of patients), invasive intervention to drain the abscess itself may become necessary. This is more common in the elderly, the immunocompromised and for very large abscesses (>6 cm). Options include surgical resection of affected lung *via* open thoracotomy or video-assisted thoracoscopy, image-guided percutaneous drainage, or endobronchial drainage for central abscesses.

Other indications for surgical intervention include presence of a localised obstructing malignancy or life-threatening complications such as intractable haemoptysis, bronchopleural fistula or empyema. The associated perioperative mortality is 16%.

Image-guided percutaneous drainage under local anaesthetic (using CT, ultrasound or fluoroscopy) is preferred in those with comorbidities and is successful in 84% of cases. Potential complications include bronchopleural fistulae, haemothorax and empyema.

Endobronchial drainage is not commonly used for drainage of lung abscesses, particularly if the abscess if large, due to the risk of asphyxiation and respiratory compromise. Success has, however, been described in selected patients.

Outcome

Lung abscesses are associated with a 10% mortality rate. The elderly or immunocompromised and those with large abscesses (>6 cm), underlying malignancy, malnutrition, or a delay in diagnosis and treatment have a particularly poor outcome.

Further reading

- Bedawi EO, *et al.* (2018). Recent developments in the management of pleural infection: a comprehensive review. *Clin Respir J*; 12: 2309–2320.
- Corcoran J, *et al.* (2015). Pleural infection: past present and future directions. *Lancet Respir Med*; 3: 563–577.
- Davies CWH, *et al.* (2010). The British Thoracic Society Guidelines for the management of pleural infection. *Thorax*; 58: Suppl.2, ii18–ii28.
- Grijalva CG, *et al.* (2011). Emergence of parapneumonic empyema in the USA. *Thorax*; 66: 663–668.
- Hassan M, *et al.* (2018). Lung abscess or empyema? Taking a closer look. *Thorax*; 73: 887–889.
- Hooper CE, *et al.* (2015). Pleural Irrigation Trial (PIT): a randomised controlled trial of pleural irrigation with normal saline *versus* standard care in patients with pleural infection. *Eur Respir J*; 46: 456–463.
- Kioumis IP, *et al.* (2018). Lung abscess. http://bestpractice.bmj.com/best-practice/monograph/927/highlights/summary.html.
- Kuhajdaa I, *et al.* (2015). Lung abscess – aetiology, diagnostic and treatment options. *Ann Trans Med*; 3: 183.
- Lui MMS, *et al.* (2016). Complications of indwelling pleural catheter use and their management. *BMJ Open Respir Res*; 3: e000123.
- Maskell NA, *et al.* (2012). RAPID score – the first validated clinical score in pleural infection to identify those at risk of poor outcome at presentation. *Am J Respir Crit Care Med*; 185: A5341.
- Maskell NA, *et al.* (2006). The bacteriology of pleural infection by genetic and standard methods and its mortality significance. *Am J Respir Crit Care Med*; 174: 817–823.
- Menzies SM, *et al.* (2011). Blood culture bottle culture of pleural fluid in pleural infection. *Thorax*; 66: 658–662.
- Peña Griñan N, *et al.* (1990). Yield of percutaneous needle lung aspiration in lung abscess. *Chest*; 97: 67–94.
- Picollo F, *et al.* (2014). Intrapleural tissue plasminogen activator and deoxyribonuclease for pleural infection. An effective and safe alternative to surgery. *Ann Am Thorac Soc*; 11: 1419–25.
- Rahman NM, *et al.* (2011). Intrapleural use of tissue plasminogen activator and DNase in pleural infection. *N Engl J Med*; 365: 518–526.
- Van Sonnenberg E, *et al.* (1984). Lung abscess: CT guided drainage. *Radiology*; 151: 337–341.
- Yu H (2011). Management of pleural effusion, empyema and lung abscess. *Semin Interv Radiol*; 28: 75–86.

Endoscopic lung volume reduction

Ralf Eberhardt and Maren Schuhmann

In patients with severe COPD and advanced emphysema, the emphysematous destruction of the lung leads to both a reduction of the gas exchange surface and to hyperinflation. The increased residual volume (RV), as an expression of static hyperinflation, increases even more disproportionately during exercise, resulting in a high end-expiratory lung volume followed by shortness of breath and reduced exercise capacity in these patients.

Although medical therapy and pulmonary rehabilitation aim to relieve symptoms, the quality of life (QoL) of patients with severe emphysema is still limited. Any therapy strategies therefore have to aim for a significant reduction of the hyperinflation and lung volume in order to improve respiratory mechanics, physical activity and even symptoms.

Lung volume reduction surgery

Lung volume reduction surgery (LVRS) with resection of one-third of a lung lobe on each side can reduce the volume of the hyperinflated lung. It was shown that LVRS has the potential to improve pulmonary function, 6-min walking distance (6MWD) and QoL in selected patients. Furthermore, patients with upper lobe predominant emphysema and a low exercise capacity prior to surgery have a survival benefit after LVRS. However, the high post-operative mortality of up to 7.9% and the high morbidity, including respiratory failure and prolonged air leakage, made it necessary to develop minimally invasive approaches for lung volume reduction. Nowadays, various endoscopic techniques are available to achieve this objective.

Key points

- Lung volume reduction can improve pulmonary function, exercise capacity and quality of life in patients with COPD and severe emphysema.
- Beside lung volume reduction surgery, various techniques of endoscopic lung volume reduction are now available to reproduce this treatment option in a minimally invasive way.
- In cases without collateral ventilation, endoscopic valve placement should be considered; in addition, lung volume reduction coil placement and bronchoscopic thermal vapour ablation are further possibilities in the treatment of selected patients.

Endoscopic lung volume reduction

The interventional methods for endoscopic lung volume reduction (ELVR) are divided into blocking and nonblocking devices.

- Blocking devices: intrabronchial valves (IBVs) and endobronchial valves (EBVs)
- Nonblocking devices: implantation of nitinol lung volume reduction coils (LVRCs) and treatment with vapour or polymeric glue

Endoscopic valve placement

Endoscopic valve placement *via* the working channel of a flexible bronchoscope is the most commonly used technique with the highest evidence level to date. Two different types are commercially available. IBVs (Spiration; Olympus, Tokyo, Japan) and EBVs (Zephyr; Pulmonx, Inc., Neuchatel, Switzerland) have different shapes but do not differ in their function of acting as one-way valves. Both block the inspired air into the treated lobe while air and secretions can escape during expiration (figure 1a and b). Although IBVs were originally used for bilateral treatment with incomplete occlusion, unilateral placement with complete occlusion of the most destroyed lobe has become the preferred technique for both types of valves. This way, maximal lung volume reduction can be achieved by causing complete atelectasis of the treated lobe (figure 1c).

In the first randomised controlled trial (RCT) of unilateral EBV treatment, improvements in FEV_1, 6MWD and QoL were observed. These modest changes were statistically significant but not clinically meaningful. However, the subgroup of patients with complete fissures on CT showed a better outcome in this trial because fissure integrity on CT scan analysis is a surrogate for low or absent collateral ventilation (CV). CV describes airflow through parenchymal bridges between the treated and the untreated lobe, and this will offset the effect of valve therapy. Besides the CT assessment, CV can also be measured endoscopically by using the Chartis system (Pulmonx, Inc.). After blocking a lobe bronchus with a balloon, the airflow from the target lobe decreases and stops in patients without significant CV.

Therefore, IBV or EBV treatment is now only suggested in CV-negative patients. After taking this criterion into account, the latest RCTs showed clinically meaningful improvements in all endpoints, such as changes in pulmonary function testing (PFT), 6MWD and QoL. A mean increase in FEV_1 of >20% and an increase of 33–79 m in the 6MWD can be expected. Although the interindividual variability in the response is high, 60% of treated patients meet the minimal clinically important difference (MCID) in the various parameters.

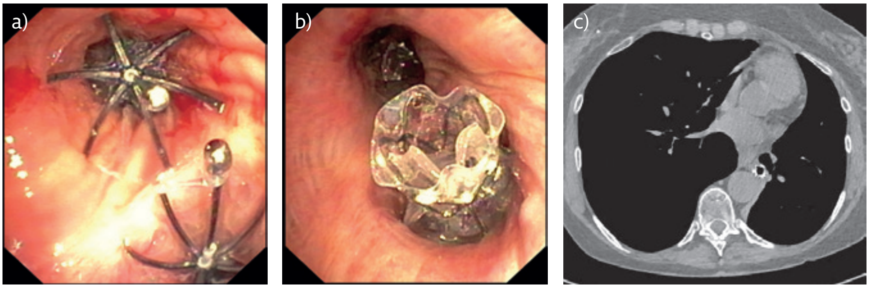


Figure 1. a) IBVs in the left upper lobe; b) EBVs in the left lower lobe; c) corresponding CT image with complete atelectasis of the treated left lower lobe.

In contrast to LVRS, endoscopic valve placement is also possible in patients with lower lobe predominant or homogeneous emphysema. While the outcome in patients with upper or lower lobe predominant emphysema does not differ, patients with homogeneous emphysema distribution might benefit a little less from EBV treatment.

Even though endoscopic valve placement is a minimally invasive procedure with a good safety profile, it is not without complications. The most common complication is a post-interventional pneumothorax, which appears most frequently in the first 3 days after the intervention and can be life-threatening for the patients. After a rapid volume reduction of the treated lobe, the ipsilateral lobe expands to fill the void. In ~20% of treated patients, this leads to a tear in the untreated lobe with collapse of the lung. The pneumothorax usually requires chest tube placement, removal of one or all valves and/or a surgical intervention may become necessary to correct this procedure-related complication.

However, it appears that patients who develop complete atelectasis after valve placement show not only improvements in lung function, exercise capacity and QoL, but also in survival.

Coil implantation

Another technique for ELVR is the endoscopic implantation of nitinol coils in the lung periphery. 10–14 straightened LVRCs are inserted bilaterally into two lobes in two separate bronchoscopies. After removing the delivery catheter, the coils return to their original shape and pull the lung tissue towards the hilum (figure 2). This aims to increase the elastic recoil of the emphysematous lung and compresses the surrounding lung tissue. The advantage of this technique is that it is independent of CV. Furthermore, treatment of both upper and lower lobes as well as of

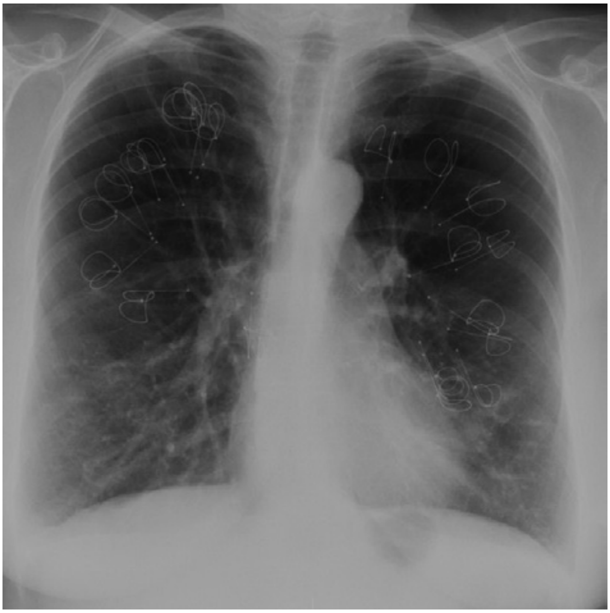


Figure 2. Bilateral treatment of both upper lobes with LVRCs.

homogeneous emphysema is possible. A complete removal of the LVRCs after they have been placed is seldom possible and hence, this technique has to be considered as irreversible.

In the largest RCT (RENEW) of coil implantation patients showed modest but statistically significant improvements in lung function, 6MWD and QoL. Although a between-group difference of 14.6 m in 6MWD and 7.0% in FEV_1 after 12 months is not clinically important, the improvement of –8.9 points in St George's Respiratory Questionnaire (SGRQ) score exceeds the threshold of the MCID. In a *post hoc* analysis, patients with a lower exercise capacity and severe hyperinflation (RV >225% predicted) had a better outcome, and future studies will have to focus on this subgroup.

Mild haemoptysis is a typical, but often temporary, complication after LVRC treatment. Therefore, patients on long-term anticoagulation should not be treated with this technique. Additional but rare complications are pneumothorax and increased rate of pulmonary infections. Although the procedure appears to be safe, a 90-day mortality of 3.5% was reported in one retrospective single-centre study, where these patients developed a refractory pneumonia in the treated lobe. It is be expected that the effect of LVRC might weaken over time.

Bronchoscopic thermal vapour ablation

The use of bronchoscopic thermal vapour ablation (BTVA) of emphysematous lung tissue is a novel and irreversible technique for ELVR. After calculating the energy based on the lung tissue mass, vapour is sprayed into the most destroyed segments endoscopically. This leads to an inflammatory reaction in the parenchyma followed by scarring of this part of the lung and then to lung volume reduction.

Originally, a complete lobe was treated in a single BTVA session but due to excessive inflammation with reported lethal outcome in some individual cases, BTVA is now split into two sessions. In a RCT with sequential treatments of separate segments in both upper lobes, the safety profile was improved without losing the positive outcome. The improvements in PFT and QoL were similar to the other ELVR techniques after 6 months (FEV_1 +14.7% and SGRQ –8.9 points).

With this stepwise technique, a segmental treatment of the most emphysematous destroyed areas of the lung (independent of any CV) has become possible, although BTVA is currently approved for upper lobe treatment only.

Other techniques

Other techniques, like polymeric lung volume reduction (PLVR) and targeted lung denervation (TLD), are being examined in clinical trials. PLVR functions in a similar way to BTVA but using polymeric glue instead of vapour for lung tissue scarring, while TLD destroys the vagal nerves of the bronchi with radiofrequency ablation. After destruction of the vagal innervation of both lungs in the main bronchi, the peripheral airway obstruction is impaired. Both techniques are in an experimental phase and can be applied in clinical trials for selected patients only.

Patient selection

Proper patient selection is the key to success and good outcome after ELVR. Based on PFTs (FEV_1 <40% predicted and RV >200% predicted), exercise testing, CT scan analysis and perfusion scanning, suitable patients and the best technique have to be selected. The physicians should review the comorbidities of these seriously ill patients, and should also consider emphysema distribution and collateral ventilation.

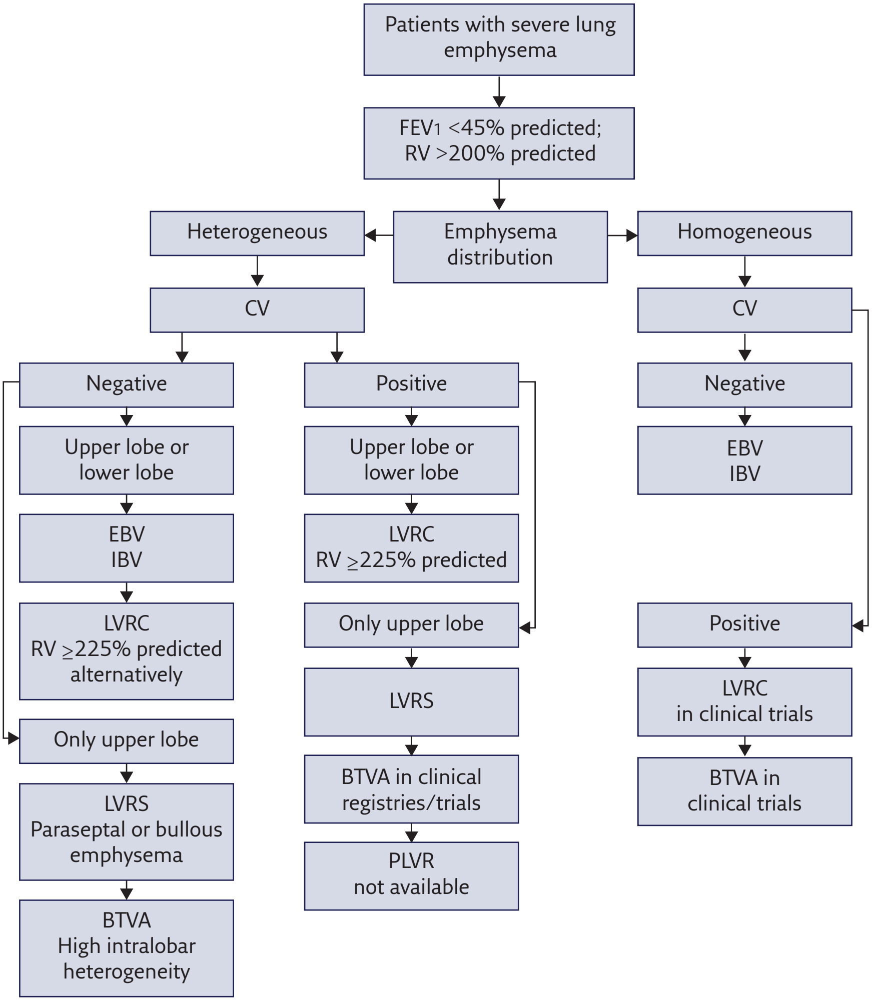

Patients with severe lung emphysema
FEV1 <45% predicted; RV >200% predicted
Emphysema distribution
Heterogeneous
Homogeneous
CV
CV
Negative
Positive
Negative
Upper lobe or lower lobe
Upper lobe or lower lobe
EBV IBV
EBV IBV
LVRC RV ≥225% predicted alternatively
LVRC RV ≥225% predicted
Only upper lobe
Positive
Only upper lobe
LVRS
LVRC in clinical trials
LVRS Paraseptal or bullous emphysema
BTVA in clinical registries/trials
BTVA in clinical trials
BTVA High intralobar heterogeneity
PLVR not available

Figure 3. Patient selection algorithm for lung volume reduction in patients with severe emphysema.

Finally, the patients should be discussed in an interdisciplinary board with radiologists, pulmonologists and thoracic surgeons, because LVRS still plays a not negligible role in the treatment of patients with severe emphysema (figure 3).

Further reading

- Eberhardt R, *et al.* (2015). Endoscopic bronchial valve treatment: patient selection and special considerations. *Int J Chron Obstruct Pulmon Dis*; 10: 2147–2157.
- Herth FJF, *et al.* (2016). Segmental volume reduction using thermal vapour ablation in patients with severe emphysema: 6-month results of the multicentre, parallel-group, open-label, randomised controlled STEP-UP trial. *Lancet Respir Med*; 4: 185–193.
- Herth FJF, *et al.* (2017). Endoscopic lung volume reduction: an expert panel recommendation – update 2017. *Respiration*; 94: 380–388.

- Kemp SV, *et al.* (2017). A multicenter randomized controlled trial of Zephyr endobronchial valve treatment in heterogeneous emphysema (TRANSFORM). *Am J Respir Crit Care Med*; 196: 1535–1543.
- Kontogianni K, *et al.* (2018). Endoscopic approaches for treating emphysema. *Expert Rev Respir Med*; 12: 1–10.
- Sciurba FC, *et al.* (2016). Effect of endobronchial coils *vs* usual care on exercise tolerance in patients with severe emphysema: the RENEW randomized clinical trial. *JAMA*; 315: 2178–2189.

Lung transplantation

Geert M. Verleden

History of lung transplantation

The first human lung transplantation was performed by Dr James Hardy in 1963 and, until the 1970's, several attempts in different centres had been performed without any long-term survival (>12 months). It was only after the introduction of cyclosporine that the first successes of heart–lung and lung transplantations were published, in the early 1980's. Since then an increasing number of lung transplantations have been performed worldwide (currently >4000 per year), in a growing number of centres.

Indications and patient selection

The aims of lung transplantation are to increase quality of life and prolong survival. In that respect, lung transplantation can be offered to patients with end-stage pulmonary or cardiopulmonary disease, for whom no other treatment options are available. Indications are: COPD with or without α_1-antitrypsin deficiency (36%); CF (15.6%) and non-CF bronchiectasis (2.7%); interstitial lung disease such as idiopathic pulmonary fibrosis (IPF) and non-idiopathic fibrosis, but also sarcoidosis, histiocytosis, lymphangioleiomyomatosis and end-stage pulmonary fibrosis associated with collagen vascular diseases (34.3%); pulmonary hypertension (4.4%); and re-transplantations (4%).

Not every patient with end-stage pulmonary disease will qualify for lung transplantation, as there are absolute and relative contraindications (table 1) and, in general,

Key points

- Lung transplantation remains the only possible treatment option for carefully selected patients with end-stage lung disease, such as COPD, CF, interstitial lung disease and pulmonary arterial hypertension.
- The most appropriate surgical procedure is based on the patient's underlying disease, donor availability and center's preference.
- Lung transplantation offers an improvement of quality of life and a median survival between 4.8 and 8.9 years, depending on the underlying indication, the surgical procedure (single lung *versus* double lung transplantation) and the center's experience.
- Chronic allograft dysfunction is the major asset prohibiting long-term survival, which occurs in about 50% of patients 5 years after the procedure.

Table 1. Contraindications for lung transplantation

Absolute contraindications
History of malignancy. A 2-year disease-free interval and a low predicted risk of recurrence may be acceptable; however, a 5-year disease-free interval is required in most cases.
Untreatable dysfunction of another organ (*e.g.* heart, liver, kidney or brain) unless combined organ transplantation can be performed.
Uncorrected atherosclerotic disease with suspected or confirmed end-organ ischaemia or dysfunction and/or coronary artery disease not amenable to revascularisation.
Acute medical instability, bleeding diathesis that is not correctable.
Chronic infection with highly virulent and/or resistant microbes that are poorly controlled pre-transplant.
Significant chest wall or spinal deformity.
Class II or III obesity (BMI $\geq$35.0 kg·m^{-2}).
Psychiatric or psychological conditions associated with the inability to cooperate with the medical/allied healthcare team, a history of or current non-adherence to medical therapy.
Absence of an adequate or reliable social support system.
Severely limited functional status with poor rehabilitation potential.
Substance abuse or dependence (*e.g.* alcohol, tobacco, marijuana).
Relative contraindications
Age >65 years in association with low physiologic reserve and/or other relative contraindications.
Class I obesity (BMI 30.0–34.9 kg·m^{-2}), particularly truncal (central) obesity or underweight with a BMI <14 kg·m^{-2}.
Severe, symptomatic osteoporosis.
Extensive prior chest surgery with lung resection.
Mechanical ventilation and/or extracorporeal life support.
Colonisation or infection with highly resistant or highly virulent bacteria, fungi and certain strains of mycobacteria.
Atherosclerotic disease burden without end-organ disease.
Diabetes mellitus, systemic arterial hypertension, epilepsy, central venous obstruction, peptic ulcer disease or gastro-oesophageal reflux, should be optimally treated before transplantation.
All absolute and relative contraindications should first be discussed with the transplant centre, as the interpretation may vary from centre to centre based on their experience.

patients should be willing to cooperate, display adequate compliance and have an adequate social support network. In some centres, there is a clear age limit for lung transplantation, taking into account the overall donor organ shortage and the fact that patients aged >65 years old have a worse prognosis after lung transplantation. It is generally advised to always contact the local transplant centre before referring a patient for possible transplantation, or before denying this treatment option.

Surgical procedure

For most diagnoses, except for chronic infectious diseases (CF and non-CF bronchiectasis) and pulmonary hypertension, both a single or a sequential single lung transplantation (SSLTx) can be performed. Over the past 10 years, however, SSLTx has emerged as the treatment of choice for all indications (>65% SSLTx), as there is some evidence that after SSLTx patients do better in terms of survival. Some centres still preferentially perform single lung transplantations (for IPF and COPD), driven by the donor organ shortage and the high waiting list mortality, for instance patients with IPF. Since the introduction of the Lung Allocation Score, which prioritises patients with IPF and CF over COPD, the latter has now reduced.

Donor organs

Donor organ shortage remains a major drawback in all solid organ transplant programmes. Donor legislation is very important to supply the need for lung transplantation. For instance, in countries with an opting out legislation, >10 lung transplantations are performed per million inhabitants, whereas in countries with an opting in legislation, this is <5 lung transplantations. Conversely, only 25% of potential organ donors may also donate lungs. This is due to the stringent donor criteria that some centres use to retrieve lungs, which are: age <40 years, non/never-smokers, perfect blood gases, no purulent sputa and a normal chest radiograph. However, by pushing the boundaries of these criteria, lung donor acceptance can increase to >40% (older donors, smoking <20 pack-years, non-ideal blood gases, no need for a perfectly normal chest radiograph), without a clear impact on the results, at least in experienced centres. Marginal donor lungs can also be reconditioned and improved by *ex vivo* lung perfusion. The use of non-heart beating donors is increasing worldwide and the results are comparable to the use of standard donors. Living-related donation also has excellent results; however, morbidity and mortality of the donor remains a problem.

Results

Survival after lung transplantation remains inferior compared to other organ transplantations (*e.g.* kidney, liver and heart). Nevertheless, the International Society for Heart and Lung Transplantation registry reports a median survival of 4.2 years in the 1990–1998 era, compared to 6.1 years in the 1999–2008 era in a cohort of >50000 transplantations. However, the median survival depends on the underlying transplant indication: for CF, the median survival is 8.9 years, for COPD (with or without α_1-antitrypsin deficiency) 5.6–6.7 years, for interstitial lung disease 4.8–6.1 years, and for re-transplantation 2.8 years. Risk factors that increase the 1-year mortality are underlying disease, era of transplantation, some donor characteristics (cytomegalovirus status, cigarette use), recipient hospitalisation and recipient ventilator dependency. Of course, the experience of the centre also plays a major role, with centres performing >30 procedures per year having better results. In such centres, 5-year survival may have increased to >75%, with a median survival across all indications of >10 years.

Causes of early death are mainly primary graft dysfunction, surgical complications and infections; late mortality (>1-year post-transplantation) is mostly due to development of chronic rejection (chronic lung allograft dysfunction (CLAD)), solid organ cancer, lymphoma, infections, cardiovascular complications and renal failure.

Post-operative problems

Primary graft dysfunction is a form of acute lung injury that may occur during the first 72 h after lung transplantation and results from ischaemia reperfusion injury. It is the major cause of early post-transplant morbidity and mortality, which, when severe, may be treated by extracorporeal membrane oxygenation and may be prevented by the use of *ex vivo* lung perfusion. Surviving patients may later develop CLAD.

Bronchial anastomotic problems still occur in up to 15% of sutures. This may rarely lead to severe complications such as dehiscence, which may be an indication for reintervention and occasionally re-transplantation. The mortality related to suture problems has been reduced to 2–3%. In most cases, the end result is a bronchial stenosis, which may be treated with bronchial dilatations and/or stenting.

Despite the use of classical immunosuppressive treatment (calcineurin inhibitor, cell cycle inhibitor and steroids) with or without induction treatment, acute cellular rejection still occurs in about 28% of the patients within the first year. This is also the main risk factor for the development of CLAD. There is no hard evidence that one immunosuppressant is better than the other to prevent acute rejection and CLAD, although in recent years the mostly commonly used triple immunosuppressive treatment consists of tacrolimus, mycophenolate mofetil and steroids. All immunosuppressive drugs have their specific complications, for instance calcineurin inhibitors (cyclosporine and tacrolimus) may induce arterial hypertension, hyperlipidaemia, diabetes and renal insufficiency. The development of solid organ cancers (bronchial, gastrointestinal, gynaecological, urological) is significantly increased after transplantation and specific attention is needed for early diagnosis and adequate treatment of skin cancer, with a yearly dermatological appointment.

Development of CLAD is one of the major problems after lung transplantation. It occurs in about 50% of patients at 5 years post-transplant and is the main cause of late mortality. It can be diagnosed when there is a progressive decline in FEV_1 of >20% compared to the best post-operative FEV_1, provided no other cause for this decline can be identified (suture stenosis, acute rejection, pleural fluid, infection). Phenotyping of CLAD has become of utmost importance over recent years, and two phenotypes have been identified. 1) The obstructive phenotype, called bronchiolitis obliterans syndrome (BOS), which is diagnosed in 70% of CLAD patients; and 2) the restrictive phenotype, called restrictive allograft dysfunction (RAS). A mixed phenotype also exists, mostly changing initially from BOS to RAS later on. The difference between the two phenotypes is very important as RAS (and also the mixed phenotype) has a much worse prognosis compared to BOS, with a median survival of 3–5 years after BOS diagnosis, but only 6–18 months after RAS diagnosis. Treatment of these conditions is difficult as no real effective drugs are available. The addition of azithromycine (250–500 mg three times per week) has been identified as the most promising drug to prevent and treat BOS, with a significant increase in survival rates in patients taking azithromycin, compared to those who don't. In selected patients, re-transplantation may offer the only possible solution; however, re-transplantation for RAS has a worse outcome compared to re-transplantation for BOS.

Further reading

- Benden C, *et al*. (2017). Therapy options for chronic lung allograft dysfunction-bronchiolitis obliterans syndrome following first-line immunosuppressive strategies: a systematic review. *J Heart Lung Transplant*; 36: 921–933.
- Chambers DC, *et al*. (2017). The Registry of the International Society for Heart and Lung Transplantation: thirty-fourth Adult Lung and Heart-Lung Transplantation Report – 2017; focus theme: allograft ischemic time. *J Heart Lung Transplant*; 36: 1047–1059.

- Kotecha S, *et al*. (2017). Continued successful evolution of extended criteria donor lungs for transplantation. *Ann Thorac Surg*; 104: 1702–1709.
- Levvey B, *et al*. (2019). Influence of lung donor agonal and warm ischemic times on early mortality: analyses from the ISHLT DCD Lung Transplant Registry. *J Heart Lung Transplant*; 38: 26–34.
- Meyer KC, *et al*. (2014). An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. *Eur Respir J*; 44: 1479–1503.
- Shah RJ, *et al*. (2018). Primary graft dysfunction (PGD) following lung transplantation. *Semin Respir Crit Care Med*; 39: 148–154.
- Verleden SE, *et al*. (2017). Chronic lung allograft dysfunction phenotypes and treatment. *J Thorac Dis*; 9: 2650–2659.
- Weill D, *et al*. (2015). A consensus document for the selection of lung transplant candidates: 2014 – an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*; 34: 1–15.

Respiratory emergencies

Maxens Decavèle, Suela Demiri and Alexandre Demoule

Acute respiratory failure (ARF) is a serious respiratory emergency and is defined by the patient's inability to ventilate adequately or provide sufficient oxygen to the blood and systemic organs. Type 1 ARF is defined as P_{aO_2} <60 mmHg or 8 kPa and type 2 ARF is defined as P_{aCO_2} >50 mmHg or 6.67 kPa (generally also associated with hypoxaemia). The main advantage of this operational definition is that it provides a clear cut-off for P_{aO_2} and P_{aCO_2}. However, this definition does not constitute a clinical definition. Clinically, ARF is generally associated with dyspnoea and clinical signs of respiratory distress (not to be confused with 'acute respiratory distress syndrome', which is a specific entity): tachypnoea, laboured breathing (use of accessory respiratory muscles, nasal flaring, chest recession), paradoxical inspiration in cases of diaphragm failure, cyanosis, encephalopathy in cases of severe hypercapnia with respiratory acidosis, and signs of sympathetic activation (sweating, tachycardia, hypertension). Acute dyspnoea is associated with higher mortality, even in the absence of respiratory distress.

Various other specific symptoms should also be considered to be respiratory emergencies, such as moderate to severe haemoptysis, a life-threatening disease in its own right that requires urgent management.

The first response to ARF consists of ensuring adequate gas exchange by providing oxygen and/or initiating mechanical ventilation. The second step consists of diagnosis, in order to provide specific treatment. ARF may result from dysfunction at any point of the respiratory system (figure 1).

Key points

- Acute respiratory failure (ARF) is a serious respiratory emergency and is defined by the patient's inability to ventilate adequately or provide sufficient oxygen to the blood and systemic organs.
- Various other specific symptoms should also be considered as respiratory emergencies, such as moderate to severe haemoptysis.
- The first response to ARF consists of ensuring adequate gas exchange by providing oxygen and/or initiating mechanical ventilation. The second step consists of diagnosis, in order to provide specific treatment.
- There are many distinct clinical settings for respiratory emergencies, as ARF may result from dysfunction at any point of the respiratory system.

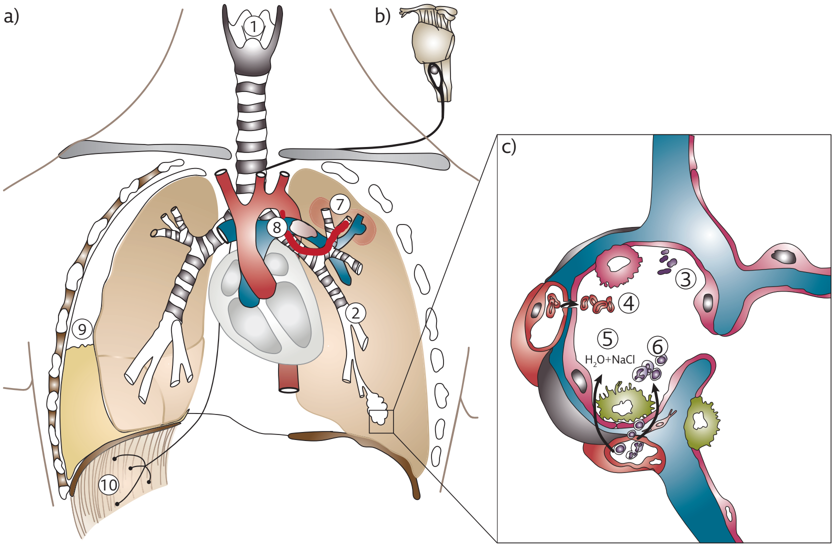


Figure 1. Anatomical representation of the respiratory system and respiratory dysfunction in 10 distinct settings: 1) upper airway obstruction; 2) lower airway disease (COPD, asthma); 3) community-acquired pneumonia; 4) diffuse alveolar haemorrhage; 5) cardiogenic pulmonary oedema; 6) infiltrative disease; 7) severe haemoptysis; 8) pulmonary embolism; 9) pleural disease; 10) neuromuscular disease. a) Main respiratory system; b) brainstem; c) lung alveoli. The authors thank Pia Chevalier (https://www.piachevalier.com) for her valuable contribution in the processing of this figure.

Diagnostic approach to ARF

Figure 2 illustrates the diagnostic approach to patients with ARF. Following physical examination, clinicians must be able to exclude ARF due to upper airway obstruction or disorders that typically present with noisy inspiratory and expiratory breathing, stridor, cough, dysphonia, agitation and a rapidly identifiable associated context, such as recent exposure to allergen (see video 1 in the online supplementary material, available at: https://books.ersjournals.com/).

Chest radiography is the second step of the diagnostic approach and allows rapid identification of easily recognisable causes of ARF, such as pneumothorax, pleural effusion, pulmonary oedema, alveolar or infiltrative pneumonia, and atelectasis (figure 2). When chest radiography is inconclusive and does not demonstrate any of these diagnoses, the third step consists of arterial blood gas analysis. Alveolar hypoventilation (P_{aCO_2} >50 mmHg) suggests the presence of acute-on-chronic respiratory failure. Elevated plasma bicarbonate is an additional argument in support of this diagnosis (indicating chronic hypoventilation). Obvious diaphragmatic dysfunction, such as hemidiaphragm elevation on chest radiography or paradoxical breathing pattern (see online supplementary material, video 2), is suggestive of neuromuscular disease, and obvious kyphoscoliosis or chest wall deformity on chest radiography is suggestive of restrictive disease and should provide crucial information on the mechanism of alveolar hypoventilation in cases of type 2 ARF (chest wall compliance alteration).

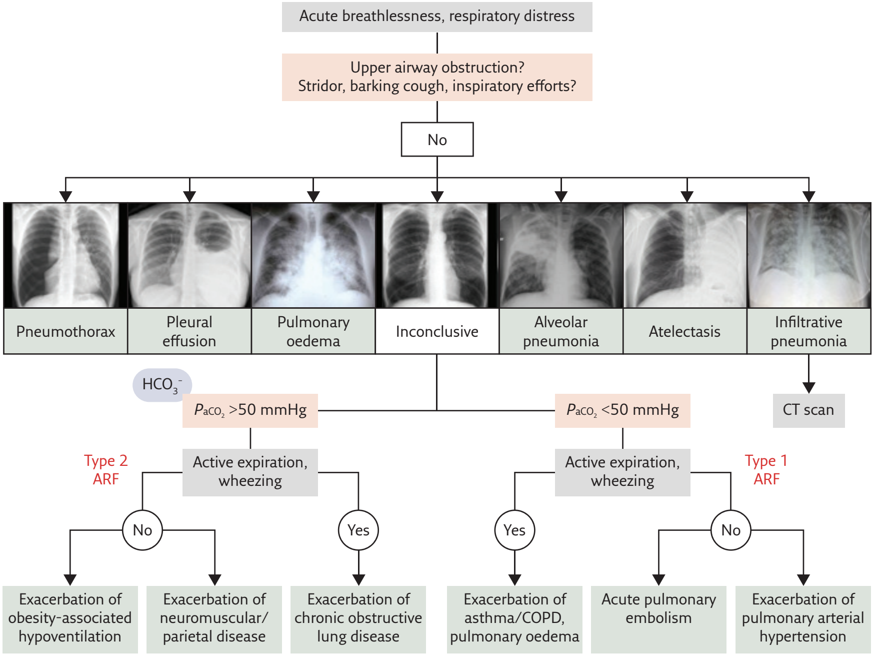

Acute breathlessness, respiratory distress
Upper airway obstruction?
Stridor, barking cough, inspiratory efforts?
No
Pneumothorax
Pleural effusion
Pulmonary oedema
Inconclusive
Alveolar pneumonia
Atelectasis
Infiltrative pneumonia
CT scan
HCO3-
PaCO2 >50 mmHg
PaCO2 <50 mmHg
Type 2 ARF
Type 1 ARF
Active expiration, wheezing
Active expiration, wheezing
No
Yes
Yes
No
Exacerbation of obesity-associated hypoventilation
Exacerbation of neuromuscular/ parietal disease
Exacerbation of chronic obstructive lung disease
Exacerbation of asthma/COPD, pulmonary oedema
Acute pulmonary embolism
Exacerbation of pulmonary arterial hypertension

Figure 2. Diagnostic approach to respiratory emergencies.

Essential aspects of clinical diagnosis and management

There are many distinct clinical settings for respiratory emergencies. 10 of these are shown in figure 1, and a summary of the most important aspects that should be considered in their diagnosis and management is given in table 1. Further details will be discussed in the following sections.

Bradykinin-mediated upper airway angio-oedema

The most common cause of acute upper airway obstruction (setting 1) in adults is upper airway angio-oedema, which can be mediated by either histamine or bradykinin. As opposed to histamine-mediated oedema, bradykinin-mediated oedema does not involve an allergic trigger, starts slowly (48–72 h), is often related to angiotensin-converting enzyme inhibitor therapy in patients with a history of recurrent oedema, and is not associated with urticaria or pruritus. Bradykinin-mediated angio-oedema is an indication for prompt specific treatment by plasma-derived or recombinant C1-inhibitor concentrate.

Severe acute exacerbation of COPD and severe exacerbation of asthma

The clinical setting of lower airway disease (setting 2) includes both severe acute exacerbation of COPD and severe exacerbation of asthma. In severe acute exacerbation of COPD, NIV should be considered when pH <7.35 (with P_{aCO_2} >45 mmHg) in the absence of contraindication. For patients requiring hospitalisation, a 5-day course of steroids should be considered in patients who do not improve after a few days and in those with a good response to steroids for a previous similar respiratory event or those with a clear history of asthma. Antibiotics should be administered to patients presenting an increase in sputum purulence or in cases of life-threatening exacerbation (*e.g.* with

Table 1. Essential aspects of clinical diagnosis and management in 10 clinical settings

Setting		Aspects of diagnosis and management
1	Upper airway obstruction (*e.g.* angio-oedema)	Distinguish bradykinin-mediated from histamine-mediated upper airway angio-oedema
2	Lower airway disease (severe acute exacerbation of COPD and severe exacerbation of asthma)	NIV, antibiotics and steroids should be administered to selected patients
3	Community-acquired pneumonia	Seven aspects to consider: *Legionella* pneumonia? *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* or *Chlamydophila psittaci*? Aspiration pneumonia? Necrotising pneumonia? ICU admission required? *Pseudomonas aeruginosa*? Early pathogen identification?
4	Diffuse alveolar haemorrhage	Diagnose vasculitis in the emergency room, since prognosis strongly depends on treatment timeliness
5	Cardiogenic pulmonary oedema	Wheezing does not inevitably mean asthma: be aware of lung congestion
6	Infiltrative disease	Distinguish acute infiltrative pneumonia from exacerbation of chronic infiltrative disease
7	Severe haemoptysis	Do not postpone bronchial artery embolisation
8	Pulmonary embolism	Accurate assessment of severity is essential to ensure optimal management
9	Pleural disease (*e.g.* tension pneumothorax)	Perform life-saving needle decompression promptly
10	Neuromuscular disease	Always consider a restrictive neuromuscular disease involving the respiratory system

a need for mechanical ventilation). In severe exacerbation of asthma, steroids should be administered to all patients, NIV is not indicated and antibiotics should only be administered in the presence of clear signs of lower respiratory tract infection.

Community-acquired pneumonia

Community-acquired pneumonia (setting 3) requires prompt and adequate initiation of antibiotics. The following seven points can guide the physician in the optimal choice of antibiotic. 1) If the clinical presentation is typical, are there any arguments in favour of *Legionella* pneumonia (*e.g.* gastrointestinal signs, acute kidney injury, delirium, myalgia, rhabdomyolysis, or water distribution system or mist machine exposure)? 2) Does the clinical presentation suggest the involvement of *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* or *Chlamydophila psittaci* (*e.g.* cutaneous eruption, haemolysis or arthralgia)? 3) Are there any arguments in favour of aspiration pneumonia (witnessed aspiration, reduced consciousness level, or pre-existing swallowing disorders)? 4) Are there any arguments in favour of necrotising pneumonia (use of nonsteroidal anti-inflammatory drugs before admission, haemodynamic failure, haemoptysis, more elevated white cell count or less response to antibiotics)? 5) Is intensive care unit (ICU) admission required? Severe community-acquired pneumonia is defined as systolic blood pressure <90 mmHg, P_{aO_2}/inspiratory oxygen fraction (F_{IO_2}) <250 or involvement of more than two lobes on chest radiography and the need for mechanical ventilation or vasopressors for >4 h, requiring ICU admission. 6) Are there any risk factors for *Pseudomonas aeruginosa*? 7) Is early pathogen identification available? Such tests should be carried out for hospitalised patients and can provide relevant information.

Diffuse alveolar haemorrhage

ARF with haemoptysis and new diffuse alveolar infiltrates on chest radiography suggest diffuse alveolar haemorrhage (DAH; setting 4). CT scans reveals ground-glass opacities and bronchoalveolar lavage confirms the cytological diagnosis of intra-alveolar haemorrhage. Antineutrophil cytoplasmic antibody (ANCA)-mediated vasculitis and anti-glomerular basement membrane (anti-GBM) disease are the main causes of immune DAH and represent rare but serious renal and respiratory emergencies. It is important to diagnose vasculitis in the emergency room, since prognosis strongly depends on treatment timeliness. Physicians should look for ear, nose and throat involvement, as well as proteinuria and acute kidney failure. The diagnosis is confirmed by the presence of ANCA and anti-GBM antibodies.

Wheezing in asthma versus *lung congestion*

A diagnosis of asthma should not be immediately considered in older patients (aged >65 years) presenting with wheezing and no personal history of asthma in childhood. In older patients, wheezing caused by bronchial oedema is the main symptom of cardiac congestion and typical signs such as crackles are often absent in cardiogenic pulmonary oedema (setting 5). Risk factors for cardiovascular disease, such as systemic arterial hypertension, are usually present. Acute exacerbation of COPD should also be considered. Physicians should be aware of a “recent” (within 5 years) diagnosis of asthma that may mask chronic heart failure, often diastolic, or COPD.

Acute infiltrative pneumonia versus *exacerbation of chronic infiltrative disease*

Patients with acute-on-chronic respiratory failure have generally been followed for months or years and present chronic symptoms such as dyspnoea. The challenge in the setting of infiltrative disease (setting 6) is to distinguish between deterioration of symptoms due to a superimposed, easy-to-treat precipitating factor (*e.g.* lower respiratory tract infection, congestion or pneumothorax), and an acute exacerbation specifically related to the underlying disease (*e.g.* idiopathic pulmonary fibrosis or sarcoidosis) requiring immunosuppressive therapy. Acute interstitial pneumonia commonly has a rapid onset (*i.e.* 3 weeks) and requires prompt diagnosis, which can be challenging due to the wide range of possible causes. Physicians must be able to conduct a rigorous diagnostic approach to identify the most common causes of exacerbation, such as pulmonary congestion, pneumocystis or viral pneumonia, drug-induced interstitial lung disease, connective tissue disease-associated interstitial lung disease, hypersensitivity pneumonitis, *etc*. Chest CT scan, followed by bronchoalveolar lavage, are essential investigations in this setting.

Severe haemoptysis

The diagnostic process for severe haemoptysis (setting 7) must comprise the following three steps. First, rule out alternative diagnoses such as gastrointestinal bleeding, epistaxis or DAH. Secondly, quantify the volume of haemoptysis: severe haemoptysis is defined as a volume >200 mL over the past 48 h, or associated ARF. Thirdly, perform CT scanning to identify the side (left or right lung) and the mechanism (bronchial arteries in 85% of cases and pulmonary arteries in 15% of cases) of the bleeding. CT scanning is also helpful to identify the cause of haemoptysis. Severe haemoptysis is an indication for prompt bronchial artery embolisation (BAE) when systemic arteries are involved. Bleeding from pulmonary arteries requires embolisation regardless of the volume of haemoptysis. Fibreoptic bronchoscopy does not have a pivotal role in the management of haemoptysis during its acute phase, but may be useful when intubation or haemostatic procedures are required (asphyxiating haemoptysis) or to guide selective intubation. Tranexamic acid could be used in association with BAE. Finally, it is worth noting that the vasoconstriction of the bronchial artery caused by terlipressin injection may hamper effective BAE by obscuring the site of bleeding and precluding artery cannulation.

Pulmonary embolism

When assessing pulmonary embolism (setting 8), accurate assessment of severity is essential to ensure optimal management. First, identify high-risk patients defined by the presence of cardiogenic shock, which requires immediate intravenous thrombolysis in the absence of contraindication. Secondly, from among the patients who are not high-risk, distinguish those at intermediate risk (defined by a simplified pulmonary embolism severity index (sPESI) >0) from those at low risk (sPESI=0). Thirdly, among intermediate-risk patients, identify intermediate-to-high-risk patients: right ventricle/left ventricle ratio >0.9 on echocardiography or CT scan and elevation of brain natriuretic peptide or cardiac troponin. These intermediate-to-high-risk patients require 48 h of observation in an intermediate care unit.

Tension pneumothorax

Two clinical presentations of tension pneumothorax (pleural disease; setting 9) can be distinguished: tension pneumothorax causing decompensation of an underlying respiratory disease, and tension pneumothorax revealed by ARF and acute right heart failure with mediastinal shift on chest radiography. Emergency treatment is similar in both cases and consists of prompt needle decompression of the chest, followed by chest tube placement and subsequent chest drainage.

Neuromuscular diseases involving the respiratory system

In patients with ARF, normal chest radiography and no known chronic respiratory disease, it is important to always consider a restrictive neuromuscular disease (setting 10). Patients generally report muscle weakness and breathlessness. Simple physical examination with neuromuscular testing should allow the diagnosis. Patients with neuromuscular disease usually present marked diaphragm dysfunction with a paradoxical breathing pattern (see online supplementary material, video 2). Most neuromuscular diseases are degenerative diseases not amenable to specific treatment. In contrast, myasthenic crisis can be reversed by timely appropriate treatment, which is why patients must be investigated for this rare disease involving the neuromuscular junction, even in the absence of any known history of neuromuscular disease.

Further reading

- Heunks L, *et al.*, eds. (2016). Pulmonary Emergencies (ERS Monograph). Sheffield, European Respiratory Society.

Lung injury and acute respiratory distress syndrome

Bernd Schönhofer and Christian Karagiannidis

Acute respiratory distress syndrome (ARDS) is the most deleterious form of acute lung injury and has high mortality rates. In 2012, an updated definition (the Berlin definition) was introduced, describing ARDS as an acute respiratory disease developing within 7 days from onset, with bilateral radiographic opacities leading to hypoxaemia. Importantly, cardiac failure must be excluded by objective assessment (*e.g.* echocardiography), while the establishment of the pulmonary artery wedge pressure being <18 mmHg, as required by previous definitions, is no longer mandatory for the diagnosis of ARDS. Figure 1 shows a typical radiograph of a patient with severe ARDS and H1N1 pneumonia requiring all adjuvant therapeutic interventions.

The exact incidence of ARDS is not known; its annual mortality rate has been estimated to be >30000 patients per year in the USA. The recent large international observational LUNG-SAFE study showed that 10% of all patients admitted to intensive care units and 23% of all patients on mechanical ventilation developed ARDS (Bellani *et al.*, 2016). However, the correct diagnosis 'ARDS' was recognised in only 51% of mild ARDS cases and 78% of severe ARDS cases. According to the Berlin definition, mild ARDS is defined as a ratio of $P\text{aO}_2$ to inspiratory oxygen fraction (F_{IO_2}) of >200 mmHg and ≤300 mmHg, moderate ARDS as $P_{\text{aO}_2}/F_{\text{IO}_2}$ >100 mmHg and ≤200 mmHg, and severe ARDS as $P_{\text{aO}_2}/F_{\text{IO}_2}$ ≤100 mmHg. By definition, the positive end-expiratory pressure (PEEP) must be >5 mmHg. Of note, ARDS criteria should be re-evaluated 24 h after onset, since their persistence is essential for the correct diagnosis of ARDS.

Key points

- Acute respiratory distress syndrome (ARDS) is an acute respiratory disease developing within 7 days from onset, with bilateral radiographic opacities leading to hypoxaemia.
- The Berlin definition for ARDS proposes classification according to severity, because of its better predictive value for mortality.
- The principles of lung-protective ventilator settings for patients with ARDS are low tidal volume (6 mL per kg ideal body weight), plateau pressure <30 cmH_2O, driving pressure <14 cmH_2O and prone positioning if $P_{\text{aO}_2}/F_{\text{IO}_2}$ <150 mmHg.
- Permissive hypercapnia may allow the achievement of protective mechanical ventilation.
- In the most severe forms of ARDS, pump-driven veno-venous extracorporeal membrane oxygenation (vv-ECMO) is a life-saving technology in experienced hands.

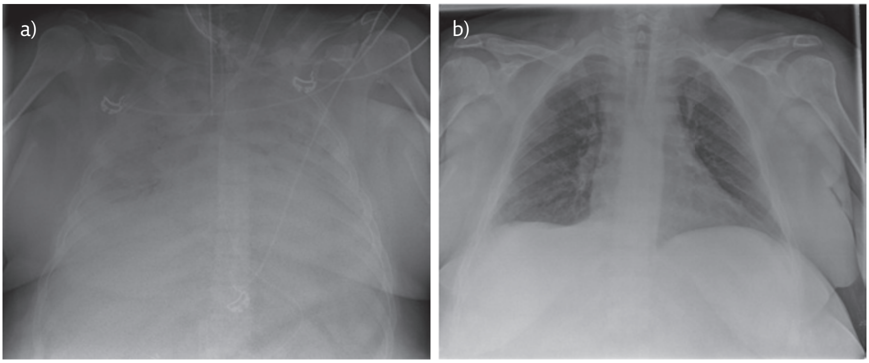


Figure 1. Radiograph of a patient with severe ARDS and H1N1 pneumonia requiring all adjuvant therapeutic interventions. Please note a) the initial white lung and b) reversibility of the disease after weeks.

ARDS may be caused by two main aetiologies: direct lung injury (*e.g.* pneumonia, aspiration, toxic inhalation, near drowning or lung contusion) or indirect lung injury (*e.g.* sepsis, burn, pancreatitis or massive blood transfusion). The two aetiologies may coexist, although pneumonia and sepsis are by far the leading causes of ARDS worldwide. Despite recent advances in the understanding of the pathophysiology of ARDS, improvements in care, and multiple therapeutic efforts directed at modifying the course of the condition, mortality rates are persistently 25–45% and in very severe forms may be even higher.

The pathophysiology of ARDS is related to altered pulmonary capillary permeability, atelectasis and increased intrapulmonary shunt, which is associated with impaired gas exchange (figure 2). The histological correlate is diffuse alveolar damage, consisting of atelectasis, intra-alveolar haemorrhage, intra-alveolar and interstitial oedema, and hyaline membrane formation. The initial phase of ARDS (exudative phase) is characterised by innate immune cell-mediated cell damage and often bacterial or viral infections. Although inflammation is a hallmark of the disease, two different phenotypes have been identified, of which the more hyperinflammatory subtype has been characterised by severe inflammation, shock and metabolic acidosis, and worse clinical outcomes. This acute exudative phase of ARDS is prone to further damage by mechanical ventilation, especially if nonprotective mechanical ventilation causes further ventilator-induced lung injury. The second, fibroproliferative, phase of ARDS is characterised by repair processes trying to restore alveolar function. Finally, in some patients, a fibrotic phase with high mortality rates may occur; a phase which may be associated with previous nonprotective ventilator settings. Moreover, ARDS is believed to cause systemic manifestations, in some cases leading to multi-organ failure and death.

In general, besides early recognition, the spectrum of ARDS treatment includes supportive care, ventilatory support and pharmacological treatment. The first and maybe most important principle of treatment is to identify potential underlying causes of ARDS. Furthermore, secondary lung injuries, such as those caused by aspiration, barotraumas, nosocomial infections and oxygen toxicity, have to be avoided. The main aims of supportive care are maintaining oxygen delivery to end-organs and optimising cardiovascular function and body fluid balance; additionally, catabolism and nutritional support have to be balanced.

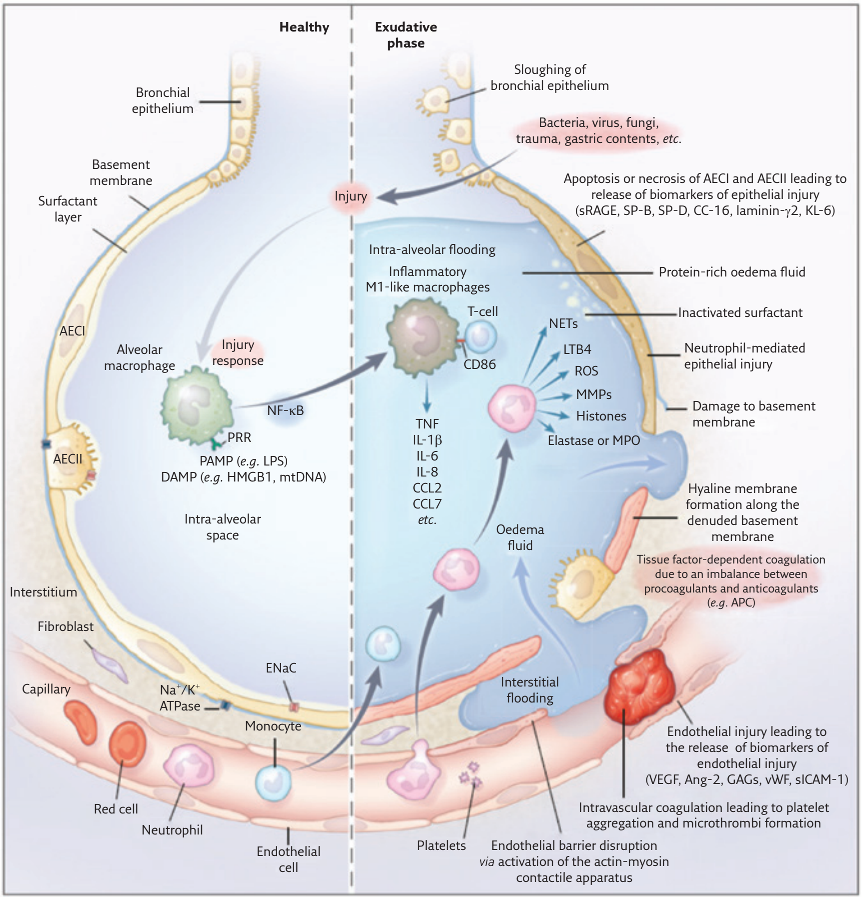

Healthy
Exudative phase
Sloughing of bronchial epithelium
Bronchial epithelium
Bacteria, virus, fungi, trauma, gastric contents, *etc.*
Basement membrane
Surfactant layer
Injury
Apoptosis or necrosis of AECI and AECII leading to release of biomarkers of epithelial injury (sRAGE, SP-B, SP-D, CC-16, laminin-γ2, KL-6)
Intra-alveolar flooding
Inflammatory M1-like macrophages
Protein-rich oedema fluid
T-cell
Inactivated surfactant
NETs
AECI
Alveolar macrophage
Injury response
CD86
LTB4
Neutrophil-mediated epithelial injury
ROS
MMPs
Damage to basement membrane
Histones
NF-κB
TNF
IL-1β
IL-6
IL-8
CCL2
CCL7
etc.
PRR
Elastase or MPO
AECII
PAMP (*e.g.* LPS)
DAMP (*e.g.* HMGB1, mtDNA)
Hyaline membrane formation along the denuded basement membrane
Intra-alveolar space
Oedema fluid
Tissue factor-dependent coagulation due to an imbalance between procoagulants and anticoagulants (*e.g.* APC)
Interstitium
Fibroblast
ENaC
Capillary
Na⁺/K⁺ ATPase
Interstitial flooding
Monocyte
Endothelial injury leading to the release of biomarkers of endothelial injury (VEGF, Ang-2, GAGs, vWF, sICAM-1)
Red cell
Intravascular coagulation leading to platelet aggregation and microthrombi formation
Neutrophil
Endothelial cell
Platelets
Endothelial barrier disruption *via* activation of the actin-myosin contactile apparatus

Figure 2. The healthy lung and the exudative phase of ARDS. The healthy lung is shown on the left, and the exudative phase of ARDS is shown on the right. Injury is initiated by either direct or indirect insults to the delicate alveolar structure of the distal lung and associated microvasculature. In the exudative phase, resident alveolar macrophages are activated, leading to the release of potent proinflammatory mediators and chemokines that promote the accumulation of neutrophils and monocytes. Activated neutrophils further contribute to injury by releasing toxic mediators. The resultant injury leads to loss of barrier function, as well as interstitial and intra-alveolar flooding. Tumour necrosis factor (TNF)-mediated expression of tissue factor promotes platelet aggregation and microthrombus formation, as well as intra-alveolar coagulation and hyaline membrane formation. AECI: type I alveolar epithelial cell; AECII: type II alveolar epithelial cell; Ang-2: angiopoietin-2; APC: activated protein C; CC-16: club cell secretory protein 16; CCL: chemokine (CC motif) ligand; DAMP: damage-associated molecular pattern; ENaC: epithelial sodium channel; GAG: glycosaminoglycan; HMGB1: high-mobility group box 1 protein; IL: interleukin; KL-6: Krebs von den Lungen 6; LPS: lipopolysaccharide; LTB4: leukotriene B4; MMP: matrix metalloproteinase; MPO: myeloperoxidase; mtDNA: mitochondrial DNA; NET: neutrophil extracellular trap; PAMP: pathogen-associated molecular pattern; PRR: pattern recognition receptor; ROS: reactive oxygen species; sICAM: soluble intercellular adhesion molecule; SP: surfactant protein; sRAGE: soluble receptor for advanced glycation end products; VEGF: vascular endothelial growth factor; vWF: von Willebrand factor. Reproduced and modified from Thompson et al. *(2017) with permission.*

Regarding mechanical ventilation and avoidance of ventilator-induced lung injury, the main goal is to improve oxygenation without increasing the iatrogenic effects caused by mechanical ventilation, which has been the main focus of ARDS research in the last 50 years. Among the methods related to the ventilatory settings, those found to be really effective (and protective) are as follows: reducing tidal volume (6 mL per kg ideal body weight); reducing driving (<14 cmH_2O) and plateau (<30 cmH_2O) pressures; applying PEEP to reduce the amount of non-aerated atelectatic lung; and prone positioning if P_{aO_2}/F_{IO_2} <150 mmHg. Permissive hypercapnia may allow the achievement of protective mechanical ventilation.

However, NIV in ARDS is still a matter of debate, since evidence is low and late intubation may cause harm. According to the recent LUNG-SAFE study, mild ARDS cases may be given NIV if the patient is stable and the respiratory drive is under control.

The ‘optimal’ setting of PEEP is a matter of debate, since several methods to adjust it have been proposed, without any clear advantages over each other. Among others, the most promising technologies of PEEP adjustment are guidance by transpulmonary pressure (by means of oesophageal balloon) and electrical impedance tomography. However, no PEEP trial has proved an evidence-based advantage of any strategy, although meta-analysis has revealed a suggestion for higher PEEP levels in more severe ARDS and lower levels in less severe forms. Furthermore, pathophysiological data have suggested that recruitment manoeuvres to open the lung with high pressures lead to increased oxygenation and, by recruiting previous atelectatic lung regions, to a better compliance of the respiratory system. However, the recent randomised controlled trial ART (Alveolar Recruitment for ARDS Trial) demonstrated a disadvantage of such a strategy, which may be attributed to barotrauma.

In the subgroup of patients with severe ARDS, prone positioning is the main adjuvant therapy to reduce mortality. Alternative methods of mechanical ventilation, including high-frequency oscillatory ventilation and airway pressure release ventilation, have not been shown to reduce mortality; indeed, high-frequency oscillatory ventilation has even been reported to worsen the outcome.

Protection of the lungs may also be provided by pump-driven veno-venous extracorporeal membrane oxygenation (vv-ECMO), which improves both oxygenation and carbon dioxide removal, and allows a highly protective low tidal volume ventilation. Recently, the EOLIA trial provided some evidence that vv-ECMO is superior over conventional treatment in the most severe forms of ARDS (Combes *et al*., 2018).

Concerning pharmacological treatments for ARDS, inhaled nitric oxide has not been found to be particularly effective and there is no clear convincing data to support the widespread use of corticosteroids in both early and late phases of ARDS. However, individual patients may respond to both treatments. Neuromuscular blockers are under current debate, since a mortality benefit was shown that may be attributed to synchrony of mechanical ventilation. However, further randomised controlled trials must confirm the initial results, since survival curves demonstrated an unusual behaviour, starting to diverge after more than 14 days from randomisation.

Finally, based on experimental models and phase I and IIa clinical trials, there are new encouraging treatment options in the pipeline targeting different key steps in ARDS pathophysiology, from closing capillary leak to stem cell therapy.

Further reading

- Bellani G, *et al.* (2016). Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*; 315: 788–800.
- Briel M, *et al.* (2010). Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA*; 303: 865–873.
- Calfee CS, *et al.* (2014). Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med*; 2: 611–620.
- Combes A, *et al.* (2018). Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med*; 378: 1965–1975.
- Famous KR, *et al.* (2017). Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. *Am J Respir Crit Care Med*; 195: 331–338.
- Ferguson ND, *et al.* (2013). High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med*; 368: 795–805.
- Guérin C, *et al.* (2013). Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*; 368: 2159–2168.
- Karagiannidis C, *et al.* (2016). Extracorporeal membrane oxygenation: evolving epidemiology and mortality. *Intensive Care Med*; 42: 889–896.
- Papazian L, *et al.* (2010). Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*; 363: 1107–1116.
- Slutsky AS, *et al.* (2013). Ventilator-induced lung injury. *N Engl J Med*; 369: 2126–2136.
- Slutsky AS, *et al.* (2016). Happy 50th birthday ARDS! *Intensive Care Med*; 42: 637–639.
- Talmor D, *et al.* (2008). Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med*; 359: 2095–2104.
- The ARDS Definition Task Force (2012). Acute respiratory distress syndrome: the Berlin Definition. *JAMA*; 307: 2526–2533.
- Thompson BT, *et al.* (2017). Acute respiratory distress syndrome. *N Engl J Med*; 377: 562–572.
- Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators. (2017). Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA*; 318: 1335–1345.

Upper airway disease

Claus Bachert

Upper airway diseases are frequent, with allergic rhinitis affecting 15–25% and chronic rhinosinusitis affecting 10–12% of the European population. Acute viral rhinosinusitis (common cold) may affect each individual two to four times a year, depending on age, environmental circumstances, exposure to infected subjects and individual susceptibility. Acute and chronic upper airway diseases may all be associated with or impact on lower airway diseases, and therefore need to be included in the diagnosis and treatment strategy of any airway manifestation (the ‘united airways’ concept). Whereas the effects of acute nasal viral infections on asthma exacerbations are well described, the impact of chronic sinus disease on the lower airways has recently been better defined based on endotyping of mucosal inflammation.

Allergic rhinitis/rhinoconjunctivitis

Epidemiology

In eight out of 10 children, allergic rhinitis/rhinoconjunctivitis (ARC) starts before the age of 16 years, with sensitisation rates of up to 50%, and ARC complaints are found in up to 30% of school children. Patients are sensitised early to food (egg, milk, wheat flour or peanuts) and later to inhalant allergens (grass and tree pollen, house dust mites, mugwort, cats and dogs, or fungi); specifically, polyclonal immune responses

Key points

- Allergic rhinitis/rhinoconjunctivitis is frequent, and affects children early in life; IgE polyclonality is linked to multimorbidity, including asthma comorbidity, and disease severity.
- Pharmacotherapy and, if insufficient, allergen immunotherapy are the cornerstones of treatment, using products with proven efficacy and safety.
- Chronic rhinosinusitis (CRS) can be subdivided into CRS without and with nasal polyps, with nasal obstruction and loss of sense of smell as hallmark symptoms.
- CRS with nasal polyps can further be differentiated into endotypes: non-, moderate and severe type-2, with increasing late-onset comorbidity.
- Prognosis of disease and treatment approaches can be personalised according to endotypes, with biologics being available in the near future.

directed against a variety of allergens are associated with multimorbidity (eczema, ARC and asthma) and more severe disease. Asthma comorbidity often also begins before the age of 16 years, with symptoms upon exposure to the allergen; allergic asthma mostly stays mild to moderate.

Clinical Features

Upon allergen contact, nasal symptoms such as sneezing, itching, rhinorrhoea, congestion and impairment of sense of smell, as well as red, itchy eyes evolve within minutes. ARC is subdivided into intermittent and persistent disease (symptoms >4 days·week^{-1} and >4 weeks, respectively) and mild to moderate-severe disease (with impact on the quality of life). ARC, causing sleep disturbance, tiredness and low mood, affects school and professional/social performance, and should therefore not be underestimated.

Diagnosis

The diagnosis of ARC is based on history, skin-prick tests with a panel of frequent allergens, and ultimately, serum specific IgE measurements and nasal/conjunctival provocation testing. Sensitisations may not be clinically relevant.

Differential diagnosis

Nonallergic rhinitis in an ill-defined disease with similar symptoms to ARC but no proof of sensitisation to common allergens. A form of nonallergic rhinitis with eosinophilia has also been described but requires nasal cytology for diagnosis. Further differential diagnoses are rhinitis medicamentosa (abuse of decongestants), rhinitis secondary to pregnancy, hypothyroidism, atrophic rhinitis, septal deviations and foreign bodies.

Therapeutic management

For ARC, oral antihistamines, nasal topical glucocorticosteroids (GCSs), and a combination of topical GCSs and a topical antihistamine (Dymista; Mylan, Hatfield, UK) represent the standard pharmacotherapy (in order of increasing efficacy). Allergen avoidance and bed covers have limited value. Allergen immunotherapy (AIT) with specific medicinal products, having shown efficacy and safety in adequately powered clinical studies, is superior to pharmacotherapy in reducing symptoms, and may be disease modifying by reducing nasal symptoms during and for 2 years after immunotherapy, and by preventing the onset of asthma symptoms. AIT with sublingual tablets or solutions, or subcutaneous injections, should only be considered for allergens with clinical relevance and may also be indicated in cases of partially controlled asthma.

Chronic rhinosinusitis

Epidemiology

The prevalence of chronic rhinosinusitis (CRS) in European countries ranges from 7% to 27%, with an average of 11%; in the USA, the prevalence was estimated to be 12%, while a further 17% met criteria for past CRS. This indicates that CRS may not necessarily persist. Approximately eight out of 10 patients suffer from CRS without (CRSsNP) and two out of 10 from CRS with nasal polyps (CRSwNP). Asthma comorbidity ranges from 5% to 70% (depending on the endotype; see later) and atopy is more frequent compared to the normal population. Notably, in CRSwNP, eight out of 10 patients report late-onset asthma. Smoking is associated with an increased risk of CRSsNP, whereas sensitivity to nonsteroidal anti-inflammatory drugs (NSAID-exacerbated respiratory disease) is more than six times more frequent in CRSwNP compared to CRSsNP. In contrast to allergic rhinitis, first signs of CRS mostly develop in the third to the sixth decade of life but may rarely already develop in adolescence.

Diagnosis

Symptoms differ considerably: whereas headache and facial pain together with nasal secretions are characteristic of CRSsNP, loss of sense of smell and taste, nasal obstruction and post-nasal drip are typical signs of CRSwNP. Persistent symptoms should lead to further diagnostic steps including nasal endoscopy recognising nasal polyps, pus and swelling in the middle meatus, and eventually to a CT of the sinuses. CT is indicated when surgery may be necessary or other diseases have to be excluded. For the diagnosis of CRS and to plan surgery, the CT should not be performed during an acute upper respiratory tract infection but rather after prior treatment with topical GCSs and antibiotics.

As patients with nasal polyposis may have aspirin sensitivity, a thorough history should be taken concerning reactions to pain medication; ultimately, a diagnostic nasal or oral challenge is indicated. Smell and taste testing complete the work-up.

Differential diagnosis

Unilateral symptoms, nasal bleeding and any deformation of the face should be examined by a specialist to exclude sinister pathologies such as tumours, fungi or autoimmune processes. A more frequent differential diagnosis of CRSwNP is inverted papilloma, which may in some cases also result in malignancies. Occupational tumours are intestinal-type adenocarcinomas in woodworkers. In children, cystic fibrosis, primary ciliary dyskinesia or immune deficiencies should be considered. Further differential diagnoses are cerebrospinal fluid leak, meningoencephalocoeles, mucocoeles, polyangiitis with granulomatosis, cocaine abuse and specific or tropical infections.

Endotypes of CRS

Using clinical signs and nasal endoscopy, CRS is subgrouped into CRSsNP and CRSwNP. However, recent evidence suggests that endotypes based on the underlying mucosal inflammation allows a better prediction of prognosis, disease recurrence and responses to treatment, as has also been shown for asthma. In Europe, about 30% of CRSsNP and 80% of CRSwNP is characterised by moderate or severe type-2 inflammation, involving Th2 cells and eosinophils, and interleukin (IL)-4, IL-5, IL-13 and IgE. From non-type-2 CRSsNP to severe type-2 CRSwNP, asthma comorbidity increases from 5% to 70%, and disease recurrence from 0% to 45% within 2 years post-surgery. A disease-modifying role has been established for *Staphylococcus aureus* in severe nasal polyp disease and comorbid asthma, characterised by the release of IL-33, and the induction of IL-5 and other type-2 cytokines by staphylococcal proteins including superantigens and serine protease-like proteins. *S. aureus* proteins also may induce polyclonal IgE synthesis. Furthermore, the type-2 biomarkers listed above also serve as therapeutic targets for currently running phase III trials of biologics. Blood eosinophils, serum IgE typically with polyclonal allergen-specific IgE and periostin have been identified as biomarkers for type-2 inflammation.

As is typical for type-2 immune reactions, the response to viruses and bacteria is inadequate; patients can suffer more often, longer and more severely from simple rhinovirus infections compared to healthy subjects, and have a deficit in defending against bacteria such as *S. aureus*.

Therapeutic management

When symptoms of CRSsNP are bothering the patient, nasal GCSs together with a macrolide antibiotic may be given for a maximum of 3 months; the risk of selecting for antibiotic resistance, and the possibility of cardiotoxicity in elderly and patients with cardiac disease need to be considered. Acute episodes of sinusitis or exacerbations of CRS are best treated with amoxicillin–clavulanic acid and in cases of strong headache, with oral GCSs. As CRS may be temporary, the indication for sinus surgery should be made with caution. However, when CRSsNP is persistent, functional endoscopic sinus surgery by a skilled surgeon can lead to long-term relief of symptoms and endoscopic signs.

In CRSwNP, topical GCSs long term treatment has been recommended before considering surgery but this delayed time-point for surgery has recently been challenged. Earlier surgery, when adequate, may prevent asthma onset. Topical GCSs should certainly be continued post-operatively for life in type-2 inflammatory reactions, as the risk of disease recurrence is high. Antibiotic treatment with doxycycline has been reported to be temporarily successful in this disease and may also be used post-operatively. Local mupirocin ointment prevents colonisation of the nostrils with *S. aureus*. Systemic oral GCS therapy has been recommended as up to four bursts of a maximum of 3 weeks per year; however, due to the accumulation of adverse event risk, systemic GCSs should be avoided whenever possible. They do not lead to any long-term effects on their own but need to be combined with nasal GCSs.

When CRS is not responsive to pharmacotherapy, surgery may be indicated; however, the mucosa-sparing surgical approach for CRSsNP often fails in bilateral nasal polyps, with a recurrence rate of 40–60% within 2 years after surgery even with further nasal GCS treatment. To answer this unmet need, the removal of the mucosa from all sinuses, including the frontal sinus, has recently been shown to decrease the risk of recurrence. Nasal mucosa including the turbinates should not be routinely removed, as the re-epithelialisation of the sinuses originates from the nasal mucosa. In any case, continuous treatment with nasal GCSs is strongly advised.

Proof-of-concept studies with monoclonal antibodies (mAbs) against IL-5, IgE and IL-4 receptor-α (blocking IL-4 and IL-13) have been successful in selected patients with CRSwNP. Phase III studies are currently underway; it is likely that one or more mAbs will receive registration for CRSwNP in the near future.

Further reading

- Bachert C, *et al.* (2018). Endotype-driven care pathways in patients with chronic rhinosinusitis. *J Allergy Clin Immunol*; 141: 1543–1551.
- Bousquet J, *et al.* (2001). Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*; 108: Suppl., S147–S334.
- Fokkens WJ, *et al.* (2012). European position paper on rhinosinusitis and nasal polyps 2012. *Rhinol Suppl*; 23: 1–298.
- Tomassen P, *et al.* (2016). Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol*; 137: 1449–1456.
- Valovirta E, *et al.* (2018). Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. *J Allergy Clin Immunol*; 141: 529–538.
- Virchow JC, *et al.* (2016). Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: a randomized clinical trial. *JAMA*; 315: 1715–1725.

Asthma

Bianca Beghé, Leonardo M. Fabbri and Paul M. O'Byrne

Asthma is a heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. Albeit that asthma is usually associated with airway hyperresponsiveness and airway inflammation, these are not necessary or sufficient to make the diagnosis. When present, in the majority of the cases, chronic airway inflammation is rather specific, characterised by an increased number of $CD4^+$ Th2 lymphocytes, eosinophils and metachromatic cells in the airway mucosa, increased thickness of the reticular layer of the epithelial basement membrane, and increased volume of airway smooth muscle, pathological abnormalities that are quite distinct from those of COPD presenting with the same degree of airflow obstruction (figure 1).

The proportion of patients with these specific asthmatic abnormalities may increase further in treatment-naïve patients, considering that most asthmatic patients are on inhaled steroids (ICS) and that ICS suppress them. However, a significant proportion of patients present with identical symptoms of asthma, have either neutrophilic or minimal inflammation (paucigranulocytic) of the airways and are usually more resistant to inhaled steroids, which makes the role of inflammation in asthma more difficult to understand.

Familial predisposition, atopy, and exposure to allergens and occupational sensitising agents are important risk factors for asthma, even though the causes of asthma – the factors responsible for the development of asthma and/or its exacerbations – often remain undetermined.

Asthma is a heterogeneous disease that, over the years, has been divided into many different clinical subtypes. These correspond to recognisable clusters of demographic, clinical and/or pathophysiological characteristics that are often called 'asthma

Key Points

- Asthma is diagnosed based on clinical history and lung function testing. Allergy testing may also have a role.
- The differential diagnosis is extensive. In particular, COPD may be difficult to distinguish from asthma.
- The goal of pharmacological asthma treatment is to achieve and maintain control of symptoms and prevention of exacerbations.
- Asthma is a chronic, lifelong disease and must therefore be managed in partnership with the patient.

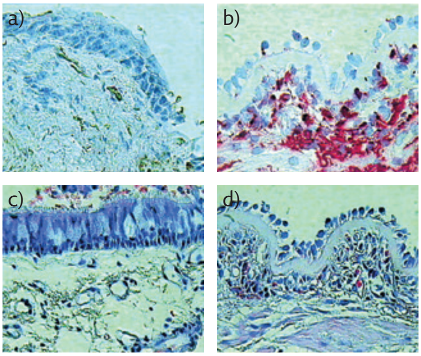


Figure 1. Photomicrographs showing bronchial biopsy specimens immunostained with anti-EG-2 (eosinophil cationic protein) a) from a patient with fixed airflow obstruction and a history of COPD, and b) from a patient with fixed airflow obstruction and a history of asthma. The two patients had a similar degree of fixed airflow obstruction. In b), there is prominent eosinophilia beneath the destroyed epithelium that is not present in a). Photomicrographs showing bronchial biopsy specimens stained with haematoxylin and eosin c) from a patient with fixed airflow obstruction and a history of COPD, and d) from a patient with fixed airflow obstruction and a history of asthma. The two patients had a similar degree of fixed airflow obstruction. In d), there is a thicker reticular layer of the epithelial basement membrane compared with c). Reproduced and modified from Fabbri et al. (2003) with permission from the publisher.

phenotypes'; however, these phenotypes do not consistently correlate strongly with specific pathological processes or treatment responses. The most common phenotypes include allergic asthma, nonallergic asthma, late-onset asthma, asthma with fixed airflow limitation and asthma with obesity.

Because of this heterogeneity, there has been a recent proposal to abolish the term 'asthma' and move to the concept of description of treatable traits; however, for practical reasons the umbrella term asthma is still recommended.

Minimum requirements for the initial diagnosis and assessment of severity of asthma

The diagnosis of asthma is based on an appropriate clinical history, together with the demonstration of variable and/or reversible airflow limitation, using symptom scores and lung function tests, particularly spirometry or peak expiratory flow (PEF). Allergy tests are also performed during the initial assessment of a patient with suspected asthma to identify possible allergic triggers, to guide their avoidance and, when appropriate, to consider specific immunotherapy.

Asthma clusters in families and its genetic determinants appear to be linked to those of other allergic IgE-mediated diseases. Thus, a personal or family history of asthma and/or allergic rhinitis, atopic dermatitis, or eczema increases the likelihood of a diagnosis of asthma.

Symptoms and medical history

Patients with asthma seek medical attention because of respiratory symptoms. A typical feature of asthma symptoms is their variability. One or more of the symptoms wheezing, chest tightness, episodic shortness of breath and/or cough are reported by >90% of patients with asthma. However, the presence of these symptoms is not diagnostic, because similar symptoms can be present with other respiratory or even cardiac diseases, or may be triggered by different stimuli in nonasthmatics (*e.g.* by acute viral infections). In some asthmatics, wheezing and chest tightness are absent, and the only symptom the patient complains of is chronic cough (cough-variant asthma).

Symptoms of asthma may be triggered or worsened by several factors, such as exercise, exposure to allergens, viral infections and emotions. Recurrent exacerbations of respiratory symptoms, worsening of lung function requiring change of treatment, unscheduled requests for medical assistance, and sometimes hospitalization are also among the characteristic clinical features of asthma.

Physical activity is an important cause of symptoms for most asthma patients, particularly in children, and for some it is the only cause. Exercise-induced bronchoconstriction usually develops not during exercise, but 5–10 min afterward, and it resolves spontaneously within 30–45 min. Prompt relief of symptoms after the use of inhaled β_2-agonist, or their prevention by pre-treatment with an inhaled β_2-agonist before exercise, supports a diagnosis of asthma.

Important aspects of personal history are exposure to agents known to worsen asthma in the home, such as dusty environments, forced air heating systems, exposure to allergens (*e.g.* pets, house dust mites or cockroaches) to which the patient is sensitised, workplace conditions, environmental tobacco smoke, or even the general environment (*e.g.* diesel fumes in traffic and seasonal aeroallergens).

Since respiratory symptoms of asthma are nonspecific, the differential diagnosis is quite extensive, and the main goal for the physician is to consider and exclude other possible diagnoses (table 1). This is even more important if the response to a trial of therapy has been negative.

While respiratory symptoms suggest asthma, the *sine qua non* condition for the objective diagnosis of asthma is the presence of respiratory symptoms and airflow obstruction that vary with time, and particularly with antiasthmatic treatment (figure 2).

Physical examination

In mild asthma, physical examination is usually normal under stable conditions, but becomes characteristically abnormal during asthma attacks. Typical physical signs of asthma attacks are wheezing on auscultation, cough, expiratory rhonchi throughout the chest, and signs of acute hyperinflation (e.g., poor diaphragmatic excursion at percussion, use of accessory muscles of respiration).

Some patients, particularly children, may present with a predominant non-productive cough. In some asthmatics, wheezing—which usually reflects airflow limitation—may

Table 1. Differential diagnosis of asthma

Localised pathology	Inhaled foreign body Endobronchial tumour Vocal cord dysfunction
Diffuse airway pathology	COPD Eosinophilic bronchitis Bronchiectasis
Other pathologies	Gastro-oesophageal reflux Left ventricular failure Pulmonary embolism Pulmonary eosinophilia

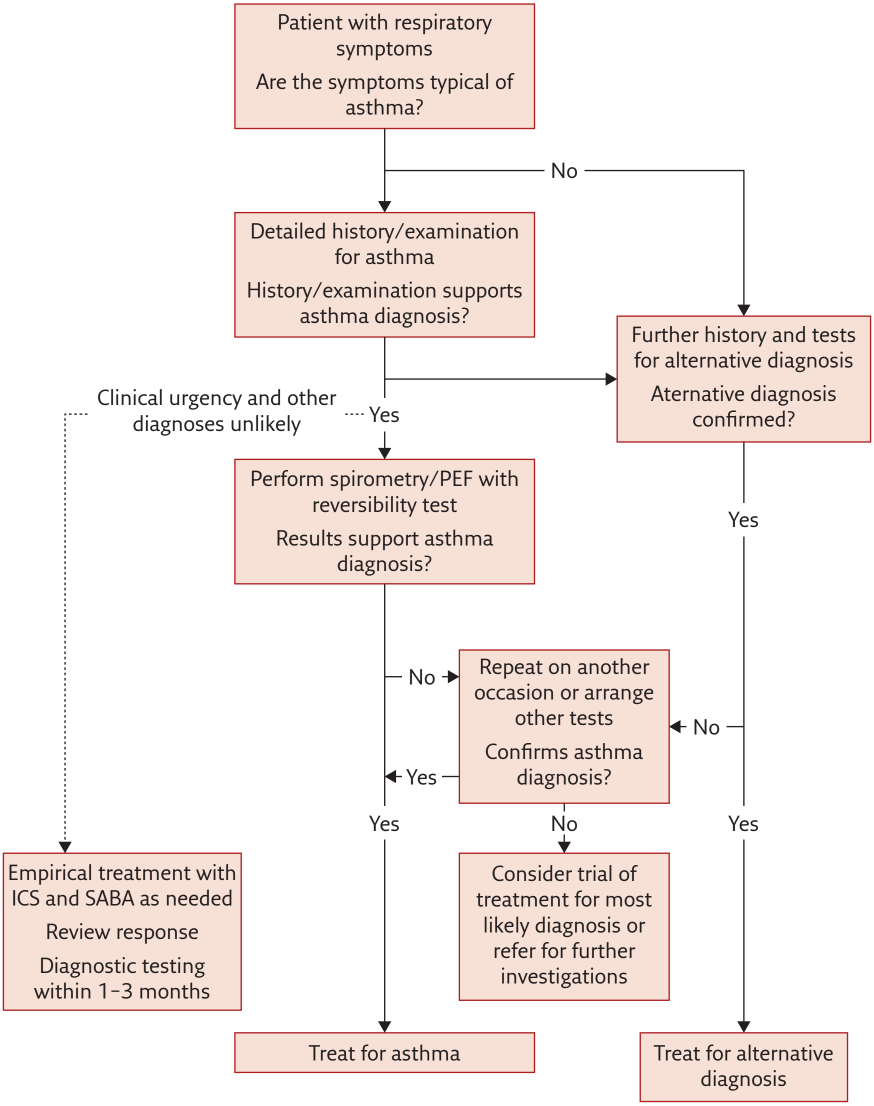

Patient with respiratory symptoms
Are the symptoms typical of asthma?
No
Detailed history/examination for asthma
History/examination supports asthma diagnosis?
Further history and tests for alternative diagnosis
Aternative diagnosis confirmed?
Clinical urgency and other diagnoses unlikely
Yes
Perform spirometry/PEF with reversibility test
Results support asthma diagnosis?
Yes
No
Repeat on another occasion or arrange other tests
Confirms asthma diagnosis?
No
Yes
Yes
No
Yes
Empirical treatment with ICS and SABA as needed
Review response
Diagnostic testing within 1–3 months
Consider trial of treatment for most likely diagnosis or refer for further investigations
Treat for asthma
Treat for alternative diagnosis

Figure 2. Diagnostic flow-chart for clinical practice: initial diagnosis. PEF should be the highest of three readings. When measuring PEF, use the same meter each time as the value may vary by up to 20% between different meters. Bronchodilator reversibility may be lost during severe exacerbations or viral infections. If bronchodilator reversibility is not present at initial presentation, the next step depends on the availability of tests and the urgency of the need for treatment. SABA: short-acting β_2*-agonist. Reproduced and modified from GINA (2018) with permission from the publisher.*

be absent or detectable only on forced expiration, even in the presence of significant airflow limitation; this may be due to hyperinflation or to very marked airflow obstruction. In these patients, however, the severity of asthma is mostly indicated by other signs, such as cyanosis, drowsiness, difficulty in speaking, tachycardia, hyperinflated chest, use of accessory muscles, and intercostal recession.

Lung function tests

Lung function tests play a crucial role in the diagnosis and follow-up of patients with asthma. Spirometric measurements (FEV_1 and vital capacity (VC) or FVC) are the standard means for assessing airflow limitation. Spirometry is recommended at the time of diagnosis and for the assessment of the severity of asthma. It should be repeated to monitor the disease and when there is a need for reassessment, such as during or after an exacerbation.

Poorly reversible or irreversible airflow limitation is usually defined by the absolute reduction of the post-bronchodilator FEV_1/FVC ratio to <0.7. However, because this parameter varies with age, it should be confirmed by post-bronchodilator FEV_1/VC values below the lower limit of normal, particularly in younger subjects.

Measurements of residual volume and TLC may be useful in assessing the degree of hyperinflation and/or enlargement of airspaces. Lung volumes may help in the differential diagnosis with COPD but are not necessary for the diagnosis, assessment of severity or differential diagnosis of asthma. In asthma, airflow limitation is usually reversible, either spontaneously or after treatment, except for moderate/severe asthma with fixed airway obstruction (see later).

An important tool for the diagnosis and subsequent treatment of asthma is the PEF meter. If spirometry does not reveal airflow limitation, then home monitoring of PEF for 2–4 weeks may help to detect an increased variability of airway calibre and assist in making the diagnosis of asthma. Daily monitoring of PEF (at least in the morning on waking and in the evening hours, preferably after bronchodilator inhalation) is also useful to assess the severity of asthma and its response to treatment, and it can help patients to detect early signs of asthma deterioration. Diurnal variability is calculated as follows:

$$\text{Diurnal variability} = \frac{100(\text{PEF}_{\text{max}} - \text{PEF}_{\text{min}})}{\text{PEF}_{\text{max}} + \frac{\text{PEF}_{\text{min}}}{2}}$$

A diurnal variability of PEF of >20% may help to confirm the diagnosis of asthma and the magnitude of the variability is broadly proportional to disease severity. PEF monitoring may be of use not only in establishing a diagnosis of asthma and assessing its severity, but also in uncovering an occupational or environmental cause for asthma. When used in this way, PEF should be measured more frequently than twice daily, and special attention should be paid to changes occurring in and out of the workplace.

Clinical and/or functional reversibility on repeated testing is required for the diagnosis of asthma. Thus, even a single reversibility test (defined as >12% and/or >200 mL reversibility in FEV_1 after bronchodilator) may help to establish the diagnosis. However, reversibility is often not present at the time of examination, particularly in patients on treatment, and thus the absence of reversibility does not exclude the diagnosis. Repeated testing of reversibility of both clinical features and functional abnormalities may be useful in obtaining the best level of asthma control achievable and/or the best lung function for individual patients. Achieving and maintaining lung function at the best possible level is one of the objectives of asthma management.

Airway hyperresponsiveness

In patients who have symptoms consistent with asthma but have normal lung function, bronchial provocation tests with methacholine, histamine or exercise are helpful in measuring airway hyperresponsiveness and thereby confirming or excluding the diagnosis of current asthma. These measurements are very sensitive but not very specific for a diagnosis of asthma, particularly when poorly reversible airflow obstruction is present. This means that while a negative test can be used to exclude a diagnosis of active asthma, a positive test does not always mean that a patient has asthma. While the measurement of airway hyperresponsiveness may be useful to confirm asthma in subjects with normal baseline lung function, it is not useful in the presence of irreversible airflow limitation, and thus in making the differential diagnosis between asthma and COPD.

Arterial blood gases

In severe asthma and, more importantly, during acute exacerbations of asthma, the measurement of arterial blood gases while the patient is breathing air and/or after oxygen administration is essential for the diagnosis of respiratory failure. This test should be performed in all patients with clinical signs of acute or chronic respiratory failure and/or HF, and in patients with an acute asthma exacerbation and PEF <50% predicted, patients who do not respond to treatment, and those with S_{aO_2} ≤92%. Moderate/severe exacerbations are usually characterised by hypoxaemia without hypercapnia; increasing associated hypercapnia is a sign of the severity of the exacerbation that makes the patient at risk of death.

Allergy tests

The presence of allergic disorders in a patient's family history should be investigated in all patients with symptoms of asthma. A history provides important information about the patient's lifestyle and occupation, both of which influence exposure to allergens, and the time and factors possibly involved in onset and exacerbations of asthma. Skin tests with all relevant allergens present in the patient's geographic area are the primary diagnostic tool in determining allergic status. Measurement of specific IgE is not usually more informative than a skin test and is more expensive. Measurement of total IgE in serum has no value as a diagnostic test for atopy. The main limitation of methods to assess allergic status is that a positive test does not necessarily mean that the disease is allergic in nature or that it is causing asthma, as some individuals have specific IgE antibodies without any symptoms, and these may not be causally involved. The relevant exposure and its relation to symptoms must be confirmed by patient history. However, in patients with confirmed severe uncontrolled allergic asthma, the measurement of total IgE is crucial to identify patients who may benefit from one of the available monoclonal antibody treatments (*e.g.* the anti-IgE, omalizumab).

Additional tests

While the diagnosis and assessment of the severity of asthma can be fully established on the basis of clinical history and lung function tests, additional tests are sometimes helpful to better characterise individual patients.

Imaging

While chest radiography may be useful to exclude diseases that may mimic asthma, it is not required in the confirmation of the diagnosis and management of asthma. The utility of chest radiography is to exclude other conditions that may imitate or complicate asthma, particularly acute asthma. Examples include pneumonia, cardiogenic pulmonary oedema, pulmonary thromboembolism, tumours (especially those that result in airway obstruction with resulting peripheral atelectasis), foreign bodies and pneumothorax.

Assessment of airway inflammation

While airway biopsies and bronchoalveolar lavage may provide useful information in research protocols, they are considered too invasive for the diagnosis or staging of asthma. In contrast, noninvasive markers of airway inflammation have been increasingly used in research protocols, particularly to differentiate asthma from COPD and measure response to treatment. These noninvasive measurements include induced sputum and exhaled nitric oxide fraction (F_{eNO}). Induced sputum and F_{eNO} are not required for establishing the diagnosis of asthma, but may be useful in the diagnosis and management of severe asthma. In particular, induced sputum helps identify the persistence of airway eosinophilia or airway neutrophilia in patients with difficult-to-treat asthma, which can be useful in deciding appropriate doses of ICS, use of specific monoclonal antibodies and reducing the risk of severe asthma exacerbations. F_{eNO} is increased in atopic asthma, but less so in nonatopic asthma, and more importantly is very sensitive to inhaled steroids, which makes it of limited help in clinical practice. Again, it is not useful in diagnosis but can be helpful in monitoring adherence to ICS, as it is effectively reduced by ICS but not by bronchodilators.

Differentiating between asthma and COPD

Both asthma and COPD are characterised by chronic airway inflammation but with very different characteristics (figure 1). In most patients, the clinical presentation and the history provide the strongest diagnostic criteria to distinguish asthma from COPD (table 2).

Results of pulmonary function tests, particularly spirometric measurements that show a nearly complete reversibility of airflow limitation, will confirm a diagnosis of asthma, and measurements that show poorly reversible airflow limitation may help to confirm the diagnosis of COPD (table 2). Differential diagnosis between asthma and COPD becomes more difficult in elderly patients, in whom some features may overlap, such as smoking and atopy, and when the patient has airflow limitation that is poorly reversible after treatment. In these cases, symptoms, lung function, airway responsiveness, imaging and even pathological findings may overlap, and thus may

Table 2. History, symptoms and results of pulmonary function tests in the differential diagnosis between asthma and COPD

	Asthma	COPD
Onset	Mainly in childhood	In mid-to-late adult life
Smoking	Often nonsmokers	Almost invariably smokers
Chronic cough and sputum	Often absent	Frequent (chronic bronchitis)
Dyspnoea on effort	Variable and reversible to treatment	Constant, poorly reversible and progressive
Nocturnal symptoms	Relatively common	Relatively uncommon
Airflow limitation	Increased diurnal variability	Normal diurnal variability
Response to bronchodilator	Good	Poor
Airway hyperresponsiveness	In most patients, with or without airflow limitation	In most patients with airflow limitation

not provide solid information to establish a diagnosis. Because an accurate diagnosis is needed to provide better treatment, it is important in these cases to undertake an individual approach and to perform additional tests. Reversibility to corticosteroids alone or in combination with long-acting bronchodilators, measurements of lung volumes and diffusion capacity, analysis of sputum and F_{eNO}, and imaging of the chest may help to demonstrate whether asthma or COPD is the predominant cause of airflow limitation in these patients (table 3).

Comorbidities of asthma

The coexistence of chronic rhinitis, nasal polyposis and sinusitis may contribute to the severity of asthma. There is evidence to show that adequate treatment of these upper airway diseases is beneficial to asthma by mechanisms that are not clearly understood. The 'one airway' concept has drawn attention to the importance of treating the whole respiratory tract when managing asthma.

Gastro-oesophageal reflux is also occasionally associated with asthma, both in adults and in children, but treatment of reflux usually has little overall effect on mild to moderate asthma.

A frequent and quite important comorbidity of asthma in adults is COPD, most likely due to smoking, which is as common in asthmatics as in the general population. Smoking modifies the airway pathology of asthma to a COPD-like pattern and reduces the response to treatment.

Comorbidities may become important in severe asthma, whereas they play a much less important role overall in the clinical manifestations of mild to moderate asthma.

Because of its complexity and heterogeneity, at the population level, asthma may be largely under- or overdiagnosed, thus the aforementioned minimum criteria for diagnosis and treatment should be used with clinical judgment in the single individual, particularly to identify treatable traits and their sensitivity to the effective antiasthma therapies that are available. This is true not only for inhaled steroids and bronchodilators, but also for the increasing number of expensive monoclonal antibodies that if properly used, may actually put and maintain under control severe asthma in patients uncontrolled by pharmacological therapy.

Table 3. Ancillary tests in the differential diagnosis between stable asthma and COPD

Ancillary test	Asthma	COPD
Reversibility to bronchodilator and/or corticosteroids	Usually present	Usually absent
Lung volumes, residual volume, TLC	Usually normal or, if increased, reversible	Usually irreversibly increased
Diffusion capacity	Normal	Decreased
Airway hyperresponsiveness	Increased	Usually not measurable due to airflow limitation
Allergy tests	Often positive	Often negative
Imaging of the chest	Usually normal	Usually abnormal
Sputum	Eosinophilia	Neutrophilia
Exhaled NO	Increased	Usually normal

Management

Considering its chronic nature and life-long duration, asthma can be effectively managed only by developing a partnership between the patient and their doctor or health professional that may provide the tools for a guided self-management, possibly written into a plan including self-monitoring, and periodic review of treatment and level of asthma control. Education plays a major role in this partnership.

While the initial treatment is calibrated on the initial assessment of severity based on history and lung function, subsequent assessment of severity is based on the level of treatment required to maintain control, and thus treatment must be adjusted in a continuous cycle of assessment, treatment, and review of the patient's response in both symptom control and future risk (of exacerbations and side-effects) (Figure 3). For individual patients, treatment decisions should also consider any patient characteristics or phenotype that predicts the patient's likelihood to respond to treatment, together with the patient's preferences and practical issues (inhaler technique, adherence and cost to the patient).

Long-term pharmacological treatment

The main aim of pharmacological treatment of asthma is to achieve and maintain current control of day-to-day symptoms (table 4), as well as preventing of the future risk of severe asthma exacerbations, while using the safest treatment options.

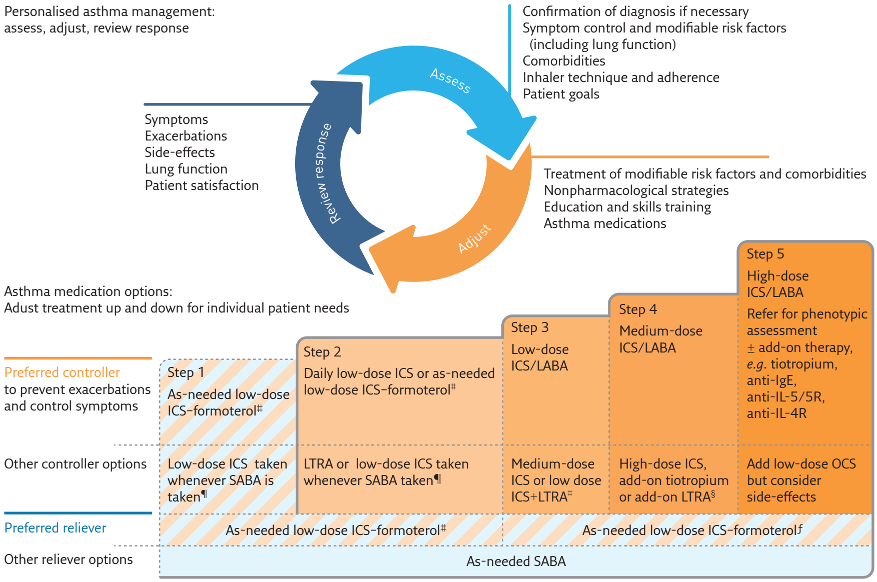

Personalised asthma management:
assess, adjust, review response
Confirmation of diagnosis if necessary
Symptom control and modifiable risk factors
(including lung function)
Comorbidities
Inhaler technique and adherence
Patient goals
Assess
Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction
Review response
Treatment of modifiable risk factors and comorbidities
Nonpharmacological strategies
Education and skills training
Asthma medications
Adjust
Asthma medication options:
Adust treatment up and down for individual patient needs
Step 5
High-dose ICS/LABA
Refer for phenotypic assessment
± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL-5/5R, anti-IL-4R
Step 4
Medium-dose ICS/LABA
Step 3
Low-dose ICS/LABA
Step 2
Daily low-dose ICS or as-needed low-dose ICS–formoterol#
Step 1
As-needed low-dose ICS–formoterol#
Preferred controller
to prevent exacerbations and control symptoms
Other controller options
Low-dose ICS taken whenever SABA is taken¶
LTRA or low-dose ICS taken whenever SABA taken¶
Medium-dose ICS or low dose ICS+LTRA#
High-dose ICS, add-on tiotropium or add-on LTRA§
Add low-dose OCS but consider side-effects
Preferred reliever
As-needed low-dose ICS–formoterol#
As-needed low-dose ICS–formoterolƒ
Other reliever options
As-needed SABA

Figure 3. Stepwise approach to control asthma symptoms and reduce risk in adults and adolescents aged 12 years or older. For children 6–11 years, the preferred step 3 treatment is low-dose ICS/LABA or medium-dose ICS. LTRA: leukotriene receptor antagonist; IL-5R: interleukin-5 receptor; #: off-label, data only with budesonide–formoterol; ¶: off-label, separate or combination ICS and SABA inhalers; §: consider adding house dust mite sublingual immunotherapy for sensitised pateints with allergic rhinitis and FEV1 >70% predicted; ƒ: low-dose ICS–formoterol as the reliever for patients prescribed budesonide–formoterol or budesonide dipropionate–formoterol maintenance and reliever therapy. Reproduced from GINA (2019) with permission from the publisher.

Table 4. GINA assessment of symptom control

In the past 4 weeks, has the patient had:

Daytime asthma symptoms more than twice a week?
Any night waking due to asthma?
Reliever needed for symptoms more than twice a week?
Any activity limitation due to asthma?

Asthma symptoms are well controlled if the patient answers 'yes' to none of these, partly controlled if the answer is 'yes' to one or two and uncontrolled if 'yes' to three or four. Reproduced and modified from GINA (2018) with permission from the publisher.

While the initial treatment should be started according to the degree of asthma control at the first visit, subsequent treatment should be adjusted according to the level of asthma control achieved (figure 3). Usually, regular treatment is lowered only after a significant period of acceptable asthma control (not less than 3 months). This means that monitoring of asthma is essential to maintain asthma control and to establish the minimal treatment requirements. Step-up and step-down of treatment is not standardised, and thus should be tailored to the individual patient to achieve and maintain optimal control with the minimum amount of medication.

Medications to treat asthma can be classified as controllers or relievers. Medications are preferably administered by inhalation, as this approach is the most effective way to treat asthma and has the fewest side-effects. Controller medications, the most effective of which are ICS, used either alone or in combination with long-acting β_2-agonist (LABA), are taken once or twice daily, on a long-term basis, to keep asthma under clinical control. In asthma, LABA should be used only in combination with ICS, when the latter are insufficient to achieve control.

Only in patients not controlled by higher doses of ICS/LABA may other secondary agents be considered. These include leukotriene receptor antagonists, theophylline, long-acting muscarinic antagonists (LAMA), systemic corticosteroids or biologic treatments (monoclonal antibodies) that target either IgE or interleukin (IL)-5.

The use of biologics must be limited to asthma patients with a history of severe exacerbations while treated with oral steroids and/or high-dose inhaled steroids plus long-acting bronchodilators (LABA/ICS and LAMA), and with an elevated serum IgE (for anti-IgE monoclonal antibody), or with elevated blood or sputum eosinophils (for anti-IL-5 monoclonal antibodies).

Reliever medications are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve asthma symptoms. These have, in the past, been almost exclusively short-acting β_2-agonists (SABA). Very recently, the use of a rapid-onset LABA (formoterol) together with an ICS from the same device, has been shown to be superior to a SABA in improving symptoms and reducing severe exacerbation risk and is now recommended as the preferred option as a reliever medication in asthma (Figure 3). If patients are adequately controlled, they should rarely need rescue medications. The use of a combination of an inhaled SABA and ICS both as controller and reliever (SMART (same maintenance and reliever therapy)) is more effective in maintaining high levels of asthma control and reducing asthma exacerbations in patients on regular LABA/ICS combination treatment plus a SABA.

Smoking asthmatics are resistant to antiasthma medications and should be primarily treated for smoking addition. Asthmatic smokers may develop features of COPD and, more importantly, are at high risk of life-threatening asthma exacerbations.

Specific immunotherapy for asthma management has limited clinical applicability as:

- it requires the identification of a single clinically relevant allergen
- it can be used safely only in mild asthma patients who are usually well controlled by pharmacotherapy
- it may be associated with severe adverse events

Treatment of exacerbations

Asthma exacerbations, manifested by increases in shortness of breath, cough, wheezing and/or chest tightness, may develop in asthma patients even when they are under regular treatment. Milder exacerbations are usually managed by an increased as-needed use of SABA or ICS/SABA. More severe exacerbations, or exacerbations that do not respond to the increased use of rescue medications, require repetitive administration of rescue medication and systemic, preferably oral, corticosteroids, and in the very severe cases, with oxygen supplementation (figure 4). Severe exacerbations require medical attention and in some instances, hospital admission.

Special considerations

Special considerations are required for patients with specific comorbidities such as (rhino) sinusitis and/or nasal polyps, aspirin-induced asthma (particularly if associated with episodes of anaphylaxis), occupational asthma and obesity. In addition, patients with asthma may require specific medical attention in cases of smoking addiction, pregnancy, surgery, infections (*e.g.* influenza epidemics) and more importantly, if asthma is severe.

Specific recommendations and algorithms

Specific recommendations and algorithms can be found in the Global Initiative for Asthma (GINA) report and related documents (www.ginasthma.org).

Further reading

- Aaron SD, *et al.* (2018). Underdiagnosis and overdiagnosis of asthma. *Am J Respir Crit Care Med*; 198: 1012–1020.
- Baur X, *et al.* (2010). Guidelines for the management of work-related asthma. *Eur Respir J*; 39: 529–545.
- Boyd SD, *et al.* (2017). Immune monitoring for precision medicine in allergy and asthma. *Curr Opin Immunol*; 48: 82–91.
- Camargo CA Jr, *et al.* (2009). Managing asthma exacerbations in the emergency department: summary of the National Asthma Education and Prevention Program Expert Panel Report 3 guidelines for the management of asthma exacerbations. *J Allergy Clin Immunol*; 124: Suppl., S5–S14.
- Chung KF (2015). Targeting the interleukin pathway in the treatment of asthma. *Lancet*; 386: 1086–1096.
- Chung KF, *et al.* (2014). International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*; 43: 343–373.
- Djukanović R, *et al.* (1992). Effect of an inhaled corticosteroid on airway inflammation and symptoms in asthma. *Am Rev Respir Dis*; 145: 669–674.
- Fabbri LM, *et al.* (2003). Differences in airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 167: 418–424.

- GINA (2018). Global Strategy for Asthma Management and Prevention. https://ginasthma.org/gina-reports/
- GINA (2019). Pocket Guide for Asthma Management and Prevention. https://ginasthma.org/gina-reports/
- Gunawardana NC, *et al.* (2018). New approaches to allergen immunotherapy. *Ann Allergy Asthma Immunol*; 151: 293–305.
- Jartti T, *et al.* (2017). Role of viral infections in the development and exacerbation of asthma in children. *J Allergy Clin Immunol*; 140: 895–906.
- Mitchell PD, *et al.* (2017). Anti-IgE and biologic approaches for the treatment of asthma. *Handb Exp Pharmacol*; 237: 131–152.
- Murphy VE, *et al.* (2017). Asthma during pregnancy: exacerbations, management, and health outcomes for mother and infant. *Semin Respir Crit Care Med*; 38: 160–173.
- Papi A, *et al.* (2018). Asthma. *Lancet*; 391: 783–800.
- Pavord ID, *et al.* (2018). After asthma: redefining airways diseases. *Lancet*; 391: 350–400.
- Peters U, *et al.* (2018). Obesity and asthma. *J Allergy Clin Immunol*; 141: 1169–1179.
- Porsbjerg C, *et al.* (2017). Co-morbidities in severe asthma: clinical impact and management. *Respirology*; 22: 651–661.
- Postma DS, *et al.* (2015). The asthma–COPD overlap syndrome. *N Engl J Med*; 373: 1241–1249.
- Thomson NC (2017). Asthma and smoking-induced airway disease without spirometric COPD. *Eur Respir J*; 49: 1602061.
- Yancey SW, *et al.* (2017). Biomarkers for severe eosinophilic asthma. *J Allergy Clin Immunol*; 140: 1509–1518.
- Zheng XY, *et al.* (2018). Regional, age and respiratory-secretion-specific prevalence of respiratory viruses associated with asthma exacerbation: a literature review. *Arch Virol*; 163: 845–853.

Bronchitis

Koliarne Tong and Peter Wark

Bronchitis is defined as airway inflammation localised to the central airways. It manifests clinically as cough, often with sputum production. Bronchitis can be either acute or chronic.

Acute bronchitis

Acute bronchitis is a common, self-limiting condition, usually seen in healthy individuals. It affects ~5% of the adult population annually. Peak incidence is during autumn and winter.

Aetiology

Most episodes of acute bronchitis are presumed to be secondary to viruses. Common viral causes of acute bronchitis include: influenza A and B, respiratory syncytial virus, parainfluenza, coronavirus and rhinovirus. Bacterial pathogens may also be associated with acute bronchitis. Commonly isolated bacteria include *Bordetella pertussis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis.* Atypical bacteria such as *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* can also cause acute bronchitis. The predisposing role of smoking and other environmental factors is unclear.

Key points

- Acute bronchitis is a common, self-limiting condition, generally seen in healthy individuals, and usually caused by a viral or bacterial infection.
- Management of acute bronchitis is largely supportive. Antibiotics have marginal benefits in reducing cough and shortening the duration of illness.
- Chronic bronchitis as a clinical syndrome is defined as a productive cough for at least 3 months per year, over two successive years.
- Smoking cessation improves mucociliary function and reduces goblet cell hyperplasia. In many patients, smoking cessation can lead to resolution of chronic bronchitis.
- Inflammation of the airway mucosa is a central feature of many respiratory diseases including asthma, COPD, bronchiectasis and chronic cough.
- Eosinophilic bronchitis is a feature of asthma, COPD and chronic cough. It appears to identify a group of patients that respond better to corticosteroid therapy.

Clinical features

Cough lasting for at least 5 days is the cardinal symptom of bronchitis. It may be accompanied by sputum production. Dyspnoea, wheeze and fever are occasionally present. Pneumonia should be excluded.

Diagnosis

The diagnosis of acute bronchitis is clinical. Chest radiography is not required unless pneumonia is suspected. Rapid viral diagnostic tests should only be performed if the result will influence management.

Treatment

Management of acute bronchitis is largely supportive. Antibiotics have marginal benefits in reducing cough and shortening the duration of illness. However, these benefits need to be weighed against the potential adverse effects and costs, including the emergence of antibiotic resistance. There is insufficient evidence to support the use of β_2-agonists, antitussives, corticosteroids or mucolytics in acute bronchitis.

Prognosis

Acute bronchitis is generally a self-limiting illness. Cough typically lasts for 10–20 days, but can last for more than 30 days in some patients, particularly in cases of *B. pertussis*. Transient bronchial responsiveness may be seen in up to 40% of cases, and usually resolves after 6 weeks. Up to a third of patients will have symptoms of chronic bronchitis in 3 years, although it is probable that these patients had predisposing factors (*e.g.* cigarette smoking) at onset of the acute illness.

Chronic bronchitis

Chronic bronchitis as a clinical syndrome is defined as a productive cough for at least 3 months per year, over two successive years. The term is most commonly used in conjunction with a diagnosis of COPD. However, it can occur independent of the presence of airflow obstruction as demonstrated by spirometry.

Pathophysiology

Mucous hypersecretion resulting in chronic or recurring productive cough are the pathological hallmarks of chronic bronchitis.

Chronic bronchitis results from chronic airway inflammation leading to airway wall remodelling, which results in mucus hypersecretion and goblet cell hyperplasia.

Cigarette smoke exposure is the best-defined cause of chronic bronchitis and is associated with airway inflammation. Chronic exposure to indoor or outdoor ambient particulate pollution is also known to have a similar effect. Viral or bacterial infections result in acute increases in mucus hypersecretion and are thought to play a crucial role in the development of chronic bronchitis.

Management

Therapies for chronic bronchitis should focus on reduction of mucus production and promotion of mucus clearance. Smoking cessation improves mucociliary function and reduces goblet cell hyperplasia. In many patients, smoking cessation can lead to resolution of chronic bronchitis. Physical activity should be encouraged. Mucolytics, such as *N*-acetylcysteine, lead to marginal reductions in exacerbation frequency. Where inflammation is associated with increased sputum eosinophils, treatment with corticosteroids improves cough and airway inflammation and reduces mucus hypersecretion.

Prognosis

The presence of chronic bronchitis without airflow obstruction is a strong predictor for the development of COPD. Chronic bronchitis without airflow obstruction is also associated with an accelerated decline in lung function and exercise tolerance, and poorer health-related quality of life. In patients with COPD, chronic bronchitis is a risk factor for increased exacerbation frequency, respiratory mortality and all-cause mortality.

Chronic airway inflammation in respiratory disease

Inflammation of the airway mucosa is a central feature of many respiratory diseases including asthma, COPD, bronchiectasis and chronic cough. Both type 1 and type 2 T-cell immunity contribute to chronic airway inflammation. Type 1 immunity is characterised by T-helper cell (Th)1 release of interleukin (IL)-1, IL-6 and interferon (IFN)-γ, whereas in type 2 immunity Th2 cells release IL-4, IL-5 and IL-13. In addition, there is increasing evidence that Th17 inflammation also leads to airway inflammation through IL-6 and IL-17 induction of Muc5AC and Muc5B.

A number of inflammatory phenotypes have been described in asthma. These include those with type 2-high inflammation, characterised by Th2 cells that release the cytokines IL-4, IL-5 and IL-13, and lead to the recruitment of eosinophils and mast cells to the airways. In childhood-onset asthma this pattern of inflammation is often associated with allergy. More recently increased airway numbers of activated innate lymphoid cells that secrete these type 2 cytokines (ILC-2 cells) have been found that are crucial in perpetuating type 2 airway inflammation. Those with type 2-high inflammation demonstrate an increase in airway eosinophils, as well other biomarkers including: peripheral blood eosinophilia, elevated fraction of exhaled nitric oxide and elevated periostin.

However, in adults with asthma, only ~50% demonstrate type 2 immune activation. Sputum studies demonstrate individuals with a neutrophilic phenotype, *i.e.* an elevation in total cell count and the proportion of neutrophils, often have an associated bacterial infection. Finally, there is a group without evidence of active bronchitis, the paucigranulocytic phenotype. Identification of the underlying inflammatory phenotype is becoming increasingly important in asthma, both in defining relative responsiveness to corticosteroids and in selecting a biological agent for severe asthma.

Similarly, heterogenous patterns of airway inflammation are seen in COPD. The primary inflammatory cells identified in stable COPD are neutrophils, macrophages and CD8$^+$ lymphocytes. However, up to 40% of patients with stable COPD have eosinophilic COPD, defined as sputum eosinophils ≥3%. Sputum eosinophilia in COPD is predictive of response to inhaled and systemic corticosteroids. *Post hoc* analyses suggest that peripheral blood eosinophilia (>2%) also predicts benefit from inhaled corticosteroid therapy. The presence of neutrophilic or eosinophilic inflammation in COPD correlates with the diversity and structure of the lung microbiome. The role of the lung microbiome in the pathogenesis of COPD remains unclear.

Non-asthmatic eosinophilic bronchitis is the cause in between 7% and 35% of patients with chronic cough. It is characterised by chronic cough and sputum eosinophilia (>3%) in the absence of variable airflow obstruction or bronchial hyperresponsiveness. In some cases, a triggering occupational exposure or inhaled allergen can be identified. Inhaled corticosteroids and allergen avoidance are the mainstays of therapy.

Further reading

- Allinson JP, *et al.* (2016). The presence of chronic mucus hypersecretion across adult life in relation to chronic obstructive pulmonary disease development. *Am J Respir Crit Care Med*; 193: 662–672.
- Bafadhel M, *et al.* (2017). Eosinophils in COPD: just another biomarker? *Lancet Respir Med*; 5: 747–759.
- Brightling CE, *et al.* (1999). Eosinophilic bronchitis is an important cause of chronic cough. *Am J Respir Crit Care Med*; 160: 406–410.
- Jónsson JS, *et al.* (1998). Acute bronchitis and clinical outcome three years later: prospective cohort study. *BMJ*; 317: 1433.
- Kim V, *et al.* (2013). Chronic bronchitis and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 187: 228–237.
- Macfarlane J, *et al.* (2001). Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. *Thorax*; 56: 109–114.
- Saetta M, *et al.* (2000). Goblet cell hyperplasia and epithelial inflammation in peripheral airways of smokers with both symptoms of chronic bronchitis and chronic airflow limitation. *Am J Respir Crit Care Med*; 161: 1016–1021.
- Siva R, *et al.* (2007). Eosinophilic airway inflammation and exacerbations of COPD: a randomised controlled trial. *Eur Respir J*; 29: 906–913.
- Smith SM, *et al.* (2014). Antibiotics for acute bronchitis. *Cochrane Database Syst Rev*; 3: CD000245.
- Sze MA, *et al.* (2015). Host response to the lung microbiome in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 192: 438–445.

COPD and emphysema

Emma Burke and John R. Hurst

COPD is an important cause of global ill-health and premature death. World Health Organization data suggest that by 2030 it will be the third commonest cause of death in the world, with the majority of those deaths occurring in low- and middle-income countries. COPD is a problem in high-income countries too, with a prevalence in adults across Europe of between 5 and 10% and an annual direct cost of over EUR 23 billion.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document is a useful resource on COPD and is regularly updated. The 2019 iteration of the GOLD document defined COPD as:

> ‘a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases’.

Aetiology and pathophysiology

COPD and emphysema arise when a genetically susceptible individual is exposed to sufficient environmental stimulus. In the developed world the most important exposure is tobacco smoke. In low- and middle-income countries household air pollution is also important. Occupational and environmental exposures may also contribute. Not everyone exposed in this way develops COPD; COPD is part of a spectrum of lung pathology that occurs in those with an underlying genetic susceptibility.

This genetic susceptibility is complex and polygenic, aside from the specific example of α_1-antitrypsin deficiency (AATD). In addition to providing a model of genetic susceptibility, it is important to detect AATD to enable appropriate monitoring for the development of liver abnormalities, and because there is increasing evidence of benefit from α_1-antitrypsin replacement (‘augmentation’) therapy. People homozygous

Key Points

- COPD and emphysema arise when a genetically susceptible individual is exposed to sufficient environmental stimulus.
- COPD is a significant cause of global morbidity and mortality, much of it in low- and middle-income countries.
- COPD is preventable and treatable: the most important intervention is exposure reduction (smoking cessation).
- Exacerbations drive morbidity and mortality and effective exacerbation prevention is a key goal of COPD guidelines.

for the Z (and null) AATD alleles may develop emphysema and airflow obstruction later in life even in the absence of significant environmental exposures. The genetic susceptibility in most people living with COPD remains unexplained.

The major site of pathology in COPD is in the small airways, resulting in airflow obstruction. Narrowing is multifactorial, including inflammatory infiltrate and airway wall remodelling. The inflammation is characterised by neutrophils and T-lymphocytes and, in more severe disease, the presence of lymphoid follicles which suggests an adaptive immune response. Note that it is normal to have inflammation in the lungs in response to smoke; the inflammation in a susceptible individual is both qualitatively and quantitatively different and can persist even after removal of the initial exposure.

When the larger airways are affected by an environmental toxin, with inflammation and hypertrophy of mucous glands, the end result is a clinical diagnosis of chronic bronchitis. Strictly, chronic bronchitis has been defined as cough productive of sputum on most days of the week for more than three consecutive months in more than two consecutive years. Emphysema is defined as permanent destruction of alveoli resulting in larger airspaces, leading to impaired gas transfer. It is a structural, anatomical diagnosis in contrast to chronic bronchitis (a clinical diagnosis) and COPD (a physiological diagnosis, as discussed in the following section).

COPD, chronic bronchitis and emphysema need not coexist. Chronic bronchitis without airflow obstruction (simple chronic bronchitis) is common and may be accepted by people living with the condition as a ‘smoker’s cough’. Chronic bronchitis does not necessarily progress to COPD.

Often, the three conditions do coexist, but to different degrees in different people. This results in people with smoking-related lung diseases appearing very heterogeneous. This has been recognised for many decades, with classic descriptions of ‘pink puffers’ (emphysema-predominant) and ‘blue bloaters’ (with cor pulmonale). A more modern way to think about this is to consider different ‘phenotypes’ of diseases. Phenotyping can encompass many features in addition to emphysema and bronchitis, for example the ‘frequent exacerbator’ or those with asthma–COPD overlap. Phenotypes may coexist and overlap. Reduction in diffusion capacity can provide an indication of emphysema. Different phenotypes may benefit from different treatments, for example volume reduction interventions in people with emphysema-predominant disease.

Diagnosis and assessment

COPD should be considered in all patients with an appropriate exposure history with symptoms of dyspnoea, cough or sputum production.

Diagnosis is confirmed by spirometry and made when an individual with an appropriate exposure history has post-bronchodilator airflow obstruction, defined by the ratio of FEV_1 to (forced or slow) vital capacity (VC) (the ‘Tiffeneau Index’).

Obstruction may be defined as a fixed FEV_1/VC ratio (<0.70), or as less than the lower limit of normal (LLN). It has been argued that using a fixed ratio is simpler, but since FEV_1/FVC declines with normal ageing, the fixed ratio tends to over-diagnose obstruction in the elderly and under-diagnose obstruction in younger populations. LLN requires knowledge of normal values in that particular population, which are not always available.

The FEV_1, expressed as a percentage of predicted, is one way to assess the severity of COPD (table 1). However, many other features contribute to severity in individual patients. In addition to spirometric severity, assessment should be made of the

Table 1. Spirometric severity of COPD

Stage	FEV1 % predicted	FEV1/(F)VC ratio
Mild	≥80%	<0.70 and/or <LLN
Moderate	≥50 and <80%	<0.70 and/or <LLN
Severe	≥30 and <50%	<0.70 and/or <LLN
Very severe	<30%#	<0.70 and/or <LLN

#: or respiratory failure.

current nature and degree of symptoms, history of exacerbations and presence of comorbidities.

The 2019 GOLD strategy classifies patients into four groups based on symptom burden and future exacerbation risk (figure 1). Symptom burden is assessed using the modified Medical Research Council (mMRC) dyspnoea scale or the COPD Assessment Test (CAT) score (an 8-point questionnaire assessing the impact of COPD).

Group A have a low symptom burden and low exacerbation risk (defined as <2 exacerbations in the previous year, and if there was one exacerbation it did not result in hospitalisation). Group B have a higher symptom burden but remain low risk. Group C are higher risk but have a low symptom burden and Group D are higher risk with greater symptoms. The proportion of people in each group varies by population studied, and by the mMRC dyspnoea scale/CAT score cut-off used. Group C tends to be the smallest.

Emphysema can be visualised using CT scanning or, when severe, be seen on a chest radiograph. Imaging is also helpful in establishing comorbid respiratory or cardiovascular diseases, and in the workup of those at risk of lung cancer and for certain treatments, such as lung volume reduction surgery or transplant. Assessment for lung volume reduction also requires an assessment of hyperinflation, measured using static lung volumes. Pulse oximetry and blood gas analysis are important in the

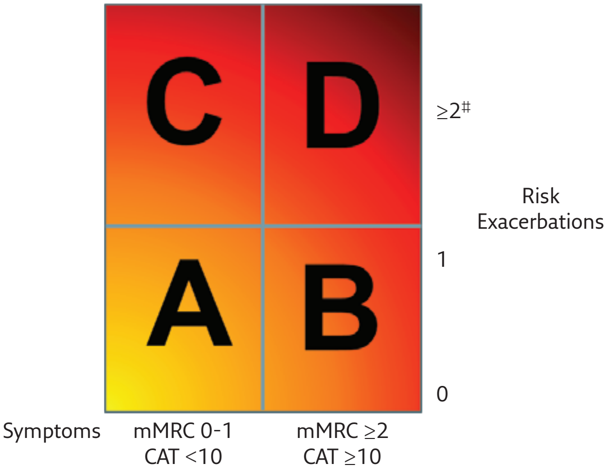


Figure 1. 2019 GOLD groups (see the text for details). #: Or one previous exacerbation if that exacerbation resulted in hospitalisation. Modified from GOLD (2019), with permission form the publisher.

detection of respiratory failure. Prognosis may best be predicted using multicomponent indices such as the BODE index, which assesses BMI, airflow obstruction, dyspnoea and exercise capacity.

Symptoms and natural history

The cardinal symptoms of COPD are productive cough (in those with chronic bronchitis) and breathlessness. Breathlessness typically does not occur until there has been significant loss of lung tissue and thus the early stages of COPD are often asymptomatic. Note that since different people have different levels of physical activity, the timing of presentation with breathlessness can be very variable. People may also first present with exacerbations, as described in more detail later in this chapter, or more rarely with another complication such as pneumothorax. Many people are living with COPD without realising they are affected, but screening has not been shown to be cost-effective. Case-finding those at risk is effective, and the diagnosis should be considered in those with symptoms and/or exacerbations and an appropriate exposure history.

Classic work by Fletcher and Peto described COPD as characterised by an accelerated lung function decline, but we now understand that the FEV1 decline rate is highly variable between individuals and may not be constant in a single individual over time. It is also apparent that some individuals never reach peak lung size (for example through premature birth or childhood environmental exposures). Therefore, some people may meet the spirometric criteria for COPD by having had a normal decline rate from sub-maximal lung growth, rather than accelerated decline from normal development (figure 2).

As the severity of airflow obstruction progresses over decades, symptoms of breathlessness typically worsen, with progressive functional limitation. In severe disease there may be respiratory failure, including the signs and symptoms of cor pulmonale and respiratory failure.

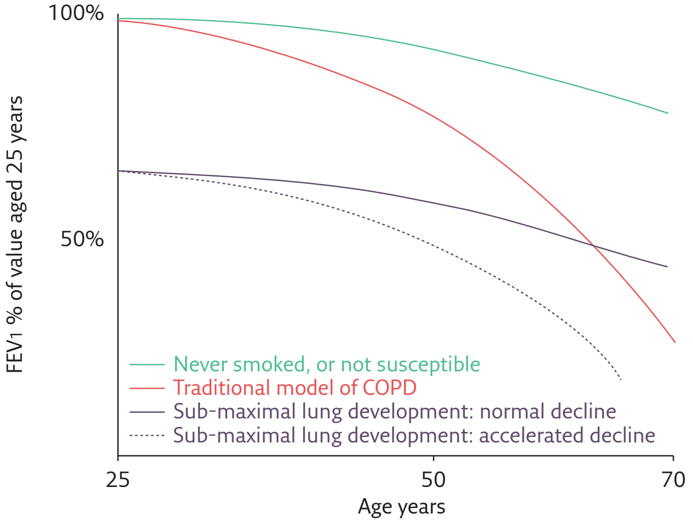


Figure 2. Disease trajectories leading to COPD. Modified from Fletcher, et al. *(1977), with permission from the publisher.*

The rate of decline in FEV_1 has previously been considered the most important way to monitor COPD, and has been a key outcome measure in clinical trials. More recent thinking about variation in this measure between individuals challenges that assertion, but it remains true that the only intervention which has definitely been shown to reduce the rate of lung function decline is smoking cessation.

Exacerbations

The natural history of COPD can be punctuated by acute deteriorations in symptoms called 'exacerbations'. An exacerbation is defined as a change in symptoms that needs a change in (COPD) treatment. In clinical practice it is important to consider and where necessary exclude other causes of symptom deteriorations in a patient with COPD, for example pneumothorax, heart failure, pulmonary embolism and pneumonia. While resulting in deterioration of symptoms, these require different treatment to an exacerbation of COPD itself, which are often driven by infection. The commonest cause of a COPD exacerbation is acquisition of a respiratory virus (most commonly human rhinovirus). They may also arise from alterations in the airway microbiome, typically with outgrowth of bacteria such as *Haemophilus influenzae*. Different people with COPD have different susceptibilities to exacerbation, and while exacerbations are more common in those with more severe disease, and track with gastro-oesophageal reflux, the best predictor of future exacerbation risk is past exacerbation history. Exacerbations, especially hospitalised ('severe') exacerbations, drive most of the healthcare cost associated with COPD, are associated with a small increase in lung function decline rate and are a major driver of impaired quality-of-life.

Management

The goals of management in COPD are to reduce symptoms, reduce exacerbations and maximise functional capacity. Through this, and preserving lung function, we can aim to increase survival.

Increasingly, COPD treatment is being guided by phenotype. Previous guidelines in which treatment was informed by FEV_1 have now been superseded. There are no specific guidelines for treatment of pure-emphysema, and decisions are generally extrapolated from the evidence available in COPD.

Reduction of environmental exposure

Reduction of environmental exposure is the most important intervention, whatever the GOLD group and is applicable to all people living with COPD. Treatment for nicotine addiction is most effective when counselling interventions are augmented by pharmacotherapy but even 'very brief advice' (ASK about smoking, ADVISE that it is harmful, ACT by supporting a quit attempt) can be effective and should be part of the core skills of anyone managing COPD. In patients with COPD and a FEV_1/FVC ratio between 65 and 70%, smoking cessation may result in normalisation of the ratio. Additional data is needed regarding the use of e-cigarettes to aid smoking cessation, and the risks of e-cigarettes over the long term.

Vaccinations against influenza and pneumococcus are generally recommended for those living with COPD.

Pharmacotherapy

The GOLD grouping becomes relevant when considering pharmacotherapy and recommending first and subsequent line therapies. The following section provides a summary of the 2019 guidance.

The A–D grouping is used when a person is first diagnosed with COPD. GOLD A will need no more than a bronchodilator, typically a short-acting β-agonist taken as needed. First-line therapy in GOLD B would be long-acting bronchodilation, either a long-acting muscarinic receptor antagonist (LAMA) alone or a long-acting β-agonist (LABA). First-line therapy in GOLD C is LAMA and in GOLD D it would be LAMA, LABA–LAMA if more symptomatic, or inhaled corticosteroid (ICS) and LABA in the context of higher blood eosinophils.

GOLD then provides two further algorithms for additional pharmacotherapy based on insufficient control of breathlessness, and insufficient control of exacerbations. This may result in escalation to so-called 'triple therapy' (ICS/LABA/LAMA, which are now available in single devices). There is increasing evidence that benefit from ICS on lung function and exacerbations can be predicted from the blood eosinophil count, although there is on-going work to define the optimal cut-offs. Targeted use of ICS is important given the potential toxicity of ICS in long-term use, especially when used at higher doses. These include the increased risk of (non-fatal) pneumonias. People with relative eosinophilia may also be those most likely to be benefit from monoclonal therapies targeting eosinophil pathways.

The three major classes of inhaled drugs, ICS, LABA and LAMA, all reduce exacerbations and improve lung function, both alone and in combination. Effects on quality of life and function are small and none have been definitively demonstrated to affect FEV_1 decline or to reduce mortality.

With inhaled therapies, appropriate device selection and training in use is key.

Long-term oral corticosteroids are not recommended in COPD. Macrolide antibiotics reduce exacerbations in COPD, at the expense of potential toxicity and the risk of resistance in the individual and society. There is limited evidence for use of older therapies such as theophylline, with some evidence that newer phosphodiesterase inhibitors such as roflumilast may help prevent exacerbations. Mucolytics may have benefit in selected populations. There is considerable interest in novel anti-inflammatory drugs, targeting specific inflammatory pathways, given that COPD is felt to be inflammatory and that this inflammation is, in general, resistant to corticosteroids.

Long-term oxygen therapy delivered for at least 15 h per 24-h period improves survival in patients with COPD and respiratory failure, defined as P_{aO_2} <7.3 kPa (<55 mmHg) breathing room air or P_{aO_2} <8 kPa (<60 mmHg) in the presence of cardiac comorbidity. For patients with hypercapnic (type 2) respiratory failure who have been admitted to hospital and required ventilatory support, home NIV reduces the risk of readmission and death.

Non-pharmacological intervention

For people with significant breathlessness, the multi-professional education and exercise class called 'pulmonary rehabilitation' is recommended as an early intervention. It reduces symptoms and exacerbation risk, and improves quality of life and/or exercise performance in most participants.

Surgical approaches include bullectomy, and volume reduction for patients with heterogeneous emphysema and gas trapping. Volume reduction can now be achieved endobronchially with valves. Transplant should be considered in patients sufficiently fit to undergo this major surgery and intensive follow-up, with prognosis from COPD typically guided by a risk-assessment score such as the BODE index.

Many people living with COPD have comorbidities, many of which are more prevalent in COPD over and above the prevalence associated with smoking. Detection and management of these is important for holistic care. Notable comorbidities include cardiovascular diseases, lung cancer, osteoporosis and mental health problems. There is evidence of sub-optimal management of some comorbidities in people living with COPD, notably under-prescription of β-blockers (which are generally safe) in COPD.

For patients with advanced disease that is symptomatic despite available therapies, it is appropriate and important to consider palliative approaches to symptom control.

Treatment of exacerbations

An increase in usual treatment is required during exacerbations. 'Mild' exacerbations are those requiring an increase in short-acting bronchodilator therapy. 'Moderate' exacerbations are treated with additional oral corticosteroids and (in the case of a suspected bacterial trigger) oral antibiotics. 'Severe' exacerbations are treated in the same way but in hospital. This classification of exacerbation severity is imperfect as it combines the severity of the underlying COPD with the severity of the additional insult. There is good evidence that shorter (5-day) courses of antibiotics and steroids are generally effective, and associated with less toxicity. Although drugs may often be given *via* a nebuliser, inhalation *via* a spacer is as effective. Treatment of respiratory failure may require supplemental oxygen and/or NIV. An exacerbation is an important opportunity to review whether appropriate exacerbation reduction interventions have been deployed.

Prognosis

Factors affecting overall prognosis in COPD are incompletely understood. Various scoring systems have been created which provide prognostic information, for example the DECAF (dyspnoea, eosinopenia, consolidation, acidaemia and atrial fibrillation) score for use at exacerbation and the BODE index for stable disease.

Further reading

- Anthonisen NR, *et al.* (1994). Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA*; 272: 1497–1505.
- Fletcher C, *et al.* (1977). The natural history of chronic airflow obstruction. *Br Med J*; 1: 1645–1648.
- GOLD (2019). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2019 report. https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf
- Hogg JC, *et al.* (2004). The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med*; 350: 2645–2653.
- Hurst JR, *et al.* (2010). Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*; 363: 1128–1138.
- Lange P, *et al.* (2015). Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med*; 373: 111–122.
- Long-Term Oxygen Treatment Trial Research Group, *et al.* (2016). A randomized trial of long-term oxygen for COPD with moderate desaturation. *N Engl J Med*; 375: 1617–1627.
- McCarthy B, *et al.* (2015). Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*; 2: CD003793.

- Murphy PB, *et al.* (2017). Effect of home noninvasive ventilation with oxygen therapy *vs* oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. *JAMA*; 317: 2177–2186.
- Pavord ID, *et al.* (2017). Mepolizumab for eosinophilic chronic obstructive pulmonary disease. *N Engl J Med*; 377: 1613–1629.
- Vestbo J, *et al.* (2011). Changes in forced expiratory volume in 1 second over time in COPD. *N Engl J Med*; 365: 1184–1192.

Exacerbations of COPD

Marc Miravitlles

Definition of exacerbation of COPD

A recent European Respiratory Society (ERS)/American Thoracic Society (ATS) guideline has clinically defined exacerbations as episodes of increasing respiratory symptoms, particularly dyspnoea, cough and sputum production, and increased sputum purulence. Patients with moderate-to-severe COPD present a mean of between one to two of these episodes per year. Patients with more advanced disease may suffer from an increasing number of exacerbations; however, some patients are more prone to suffer from exacerbations, irrespective of the severity of airflow impairment, and these are the frequent exacerbators, defined as those suffering from at least two exacerbations in the previous year. It is estimated that ~30% of patients with moderate-to-severe COPD are frequent exacerbators.

Impact of exacerbations of COPD

Exacerbations of COPD are associated with an accelerated decline in lung function and progressive impairment in health-related quality of life. An increasing number of severe exacerbations is associated with a significant reduction in survival. For all these reasons, the frequent exacerbator phenotype of COPD is particularly challenging, and the main objective of treatment is the prevention of exacerbations in order to improve clinical outcomes and survival.

Aetiology and phenotypes of exacerbations

A variety of causes may deteriorate the clinical stability of patients with COPD: cold temperature, air pollution, lack of compliance with respiratory medication, worsening of comorbidities, and pulmonary embolism, among others. The most frequent causes of exacerbations are presented in table 1.

Key points

- Exacerbations are frequent in the natural course of COPD, and up to 30% of patients are frequent exacerbators.
- There are different phenotypes of exacerbations: bacterial, viral, inflammatory (eosinophilic) and pauci-inflammatory.
- Up to two thirds of exacerbations are triggered by viral or bacterial infection.
- The relapse rate of exacerbations may be as high as 20%.
- Clinical management goals are symptomatic relief and improvement of respiratory insufficiency.

Table 1. Aetiology of exacerbations of COPD

Infective exacerbations (accounting for ~70% of all exacerbations)
- Aerobic bacteria (40–60%)
  - Frequently isolated bacteria: *Haemophilus* spp. especially nontypeable *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*
  - Bacteria associated with advanced disease and special risk factors: *Pseudomonas aeruginosa*, members of Enterobacteriaceae family (*Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Enterobacter cloacae*), *Stenotrophomonas maltophilia*
  - Others: *Staphylococcus aureus*
- Viruses (30–50%)
  - Frequently detected viruses: picornavirus (especially rhinovirus), influenza, respiratory syncytial virus
  - Infrequently detected viruses: coronavirus, parainfluenza, adenovirus, human metapneumovirus
- Atypical bacteria (5–10%)
  - *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, *Legionella* spp.
- Polymicrobial infection (20–30%)

Noninfective exacerbations (accounting for 20–40% of all exacerbations)
- Environmental factors
  - Cold air
  - Air pollution (black smoke particulate matter, sulfur dioxide, nitrogen dioxide, ozone)
  - Allergens
- Therapeutic issues
  - Noncompliance with respiratory medication
  - Abrupt withdrawal of respiratory medication
  - Possible role of comorbidities

Phenotypes of exacerbations
- Bacterial
- Viral
- Inflammatory (eosinophilic)
- Pauci-inflammatory

Recent studies have demonstrated that different types (or phenotypes) of patients with COPD experience different types or phenotypes of exacerbations. Up to four different phenotypes of exacerbations have been described: inflammatory or eosinophilic, bacterial, viral and pauci-inflammatory. Eosinophilic exacerbations are associated with increasing quantity of sputum and blood eosinophils, no significant infection in airway secretions and more bronchial hyperresponsiveness. Infective exacerbations, both bacterial and viral, are the most frequent, comprising 60–80% of exacerbations in most studies, with bacteria being responsible for three-quarters of these exacerbations. In addition, co-infection with viruses and bacteria may be frequent in patients with severe COPD and has been identified in ~25% of COPD patients admitted for an exacerbation. Interestingly, the symptoms and signs of acute exacerbation in patients with COPD have been replicated experimentally *in vivo* by infecting subjects with rhinovirus. This is a demonstration of the pathogenic role of viruses in exacerbations of COPD, both by themselves and by facilitating secondary bacterial infection. The role of bacteria in exacerbations has been a matter of controversy since the respiratory secretions of some patients with stable COPD carry significant concentrations of bacteria. Therefore, the isolation of such microorganisms during exacerbations should not always be interpreted as a definite demonstration of their pathogenic role.

However, studies performed with specific invasive techniques have shown that both the number of patients with pathogenic bacteria in respiratory secretions and their concentrations in bronchial secretions increase during exacerbations. There is no reliable biomarker of viral or bacterial exacerbation, and the best indicator of a bacterial exacerbation is still the colour of sputum. Finally, pauci-inflammatory exacerbations are associated with an increase in dyspnoea without an increase in inflammation and can be associated with a lack of compliance to medication, exposure to dust or fumes or even to comorbidities. Comorbid ischaemic heart disease is associated with longer exacerbations characterised by increased dyspnoea and wheezing, and the presence of cardiac complications is increasingly being recognised as a predictor of outcomes of COPD exacerbations.

It is interesting to point out that the type of exacerbation usually remains constant in every patient and is linked to the phenotype of COPD. Patients with asthma–COPD overlap (ACO) usually have eosinophilic exacerbations, whereas patients with chronic bronchitis and bronchiectasis more frequently present infective exacerbations. This is important for the choice of strategies aimed at treating and preventing exacerbations.

Diagnosis of exacerbations

Since there is no useful biomarker, the diagnosis of exacerbations is based on the clinical signs and symptoms. The combination of symptoms described by Anthonisen *et al*. (1987), such as increased dyspnoea and increased sputum production or purulence, have been widely used to identify exacerbations that require treatment with antibiotics. However, new studies have demonstrated that the presence of green (purulent) as opposed to white (mucoid) sputum is one of the best and easiest methods to predict bacterial aetiology and the need for antibiotic therapy.

Unfortunately, no signs or symptoms can help clinicians to differentiate bacterial from viral exacerbations. Both viral and bacterial agents may co-infect a patient with COPD, and mixed infection is associated with higher inflammation, more severe symptoms and prolonged recovery time.

The degree of airflow obstruction in COPD patients indicates the presence of different microorganisms during the course of exacerbations. Individuals with severe pulmonary function impairment, manifested by $\mathrm{FEV_1}$ <50% predicted, are at a six-fold higher risk of developing acute exacerbations caused by *Haemophilus influenzae* or *Pseudomonas aeruginosa* than patients presenting $\mathrm{FEV_1}$ >50% pred. Those with $\mathrm{FEV_1}$ <30% pred have an even higher risk for *P. aeruginosa*. Other risk factors for infection with *P. aeruginosa* include the presence of bronchiectasis, previous isolation of *P. aeruginosa* in a given patient and recent courses of antibiotics. However, the clinical presentation of exacerbation is not characteristic of any particular microorganism, and no microbiological diagnostic test is available for differential diagnosis in primary care. To date, the best biomarker available for determining a bacterial exacerbation of COPD is C-reactive protein (CRP), which can be quantified in capillary blood as a point-of-care test even in primary care.

Treatment of exacerbations of COPD

Treatment of exacerbations is based on the improvement of symptoms, basically dyspnoea, with the use of short-acting bronchodilators, without interrupting the use of background medication, usually with long-acting bronchodilators. In addition, systemic corticosteroids and antibiotics are the pillars of exacerbation treatment. Other strategies, such as oxygen therapy and noninvasive or invasive ventilation, may be required in severe patients that require hospital admission.

Antibiotics have been shown to be superior to placebo in the treatment of exacerbations, in particular when the purulence of sputum or a change in sputum colour is present. Therefore, most guidelines recommend antibiotic therapy in patients with any combination of symptoms that includes an increase in sputum purulence. Additionally, randomised, placebo-controlled, clinical trials and large observational studies have demonstrated the efficacy of antibiotics in the treatment of severe hospitalised exacerbations of COPD. Studies are ongoing to determine if patients with clear sputum can be safely treated without antibiotics in the hospital setting.

The antibiotic of choice may vary from country to country, based on the prevalence of different bacteria and, more importantly, the differences in susceptibility of the causative bacteria to antibiotics. However, the systematic sputum culture and analysis of antibiotic susceptibility is not recommended in all patients in ambulatory exacerbations and should be reserved for treatment failures and severe patients in the hospital setting.

Guidelines recommend the use of so-called first-line antibiotics, such as amoxicillin or tetracycline, in low-risk patients in countries with a low prevalence of antibiotic resistance, such as the Netherlands, the UK and other North-European countries. However, in countries with a high percentage of resistant strains or in patients with risk factors for treatment failure, the choice of an antibiotic must consider the use of amoxicillin–clavulanate and respiratory fluoroquinolones (moxifloxacin or levofloxacin) or cephalosporins (cefditoren or cefuroxime). Table 2 describes the antibiotic alternatives according to the severity of COPD.

Table 2. Risk classification and suggested antimicrobial therapy

	FEV1 % pred	Most frequent microorganisms	Suggested treatment
Mild-to-moderate COPD without risk factors	>50	*Haemophilus influenzae* *Moraxella catarrhalis* *Streptococcus pneumoniae* *Chlamydophila pneumoniae* *Mycoplasma pneumoniae*	Amoxicillin Tetracycline In areas of high incidence of resistance: amoxicillin–clavulanate, cefditoren, cefuroxime
Mild-to-moderate COPD with risk factors[#]	>50	*Haemophilus influenzae* *Moraxella catarrhalis* PRSP	Amoxicillin–clavulanate Moxifloxacin/levofloxacin Cefditoren Cefuroxime
Severe COPD	30–50	*Haemophilus influenzae* *Moraxella catarrhalis* PRSP Enteric Gram-negative bacteria	Amoxicillin–clavulanate Moxifloxacin/levofloxacin
Very severe COPD	<30	*Haemophilus influenzae* PRSP Enteric Gram-negative bacteria *Pseudomonas aeruginosa*	Moxifloxacin/levofloxacin Ciprofloxacin if *Pseudomonas* is suspected Amoxicillin–clavulanate (if allergic to quinolones)[¶]

PRSP: penicillin-resistant *S. pneumoniae*. [#]: risk factors are older age, significant cardiac comorbidity and frequent past exacerbations/admissions for COPD; [¶]: in the case of intravenous therapy, other antibiotics can be used, such as piperacillin-tazobactam, imipenem or cefepime.

Exacerbations associated with severe dyspnoea and those with an inflammatory (eosinophilic) phenotype should be treated with systemic corticosteroids. A short course of oral corticosteroids has been demonstrated to accelerate recovery from exacerbations and reduce the rate of relapse in patients with moderate-to-severe COPD. Patients can be treated with $0.5\ \mathrm{mg \cdot kg^{-1} \cdot day^{-1}}$ of methylprednisolone or equivalent in a single morning dose for 5–10 days. Treatment for >10 days has not been demonstrated to be more beneficial and increases the likelihood of adverse side-effects. Inhaled bronchodilators, particularly short-acting inhaled β_2-agonists, must be given at increased doses during exacerbations. Short-acting bronchodilators may be prescribed with a chamber of inhalation or by nebulisation. In the acute phase, repeated doses every 30–60 min can be administered with close monitoring of clinical signs and arterial gas exchange with a pulse oximeter. If prompt response to these drugs does not occur, the addition of an anticholinergic is recommended.

Oxygen therapy should be provided in cases of hypoxaemia. Adequate levels of oxygenation are P_{aO_2} >8.0 kPa or >60 mmHg, or S_{aO_2} >90%. These levels are easy to achieve in uncomplicated exacerbations. When oxygen is started, arterial blood gases should be checked 30–60 min later to ensure satisfactory oxygenation without CO_2 retention or acidosis.

The clinical and gasometric evolution of a patient will guide the decision to step down the treatment and discharge the patient from the emergency department or hospital. Family and home support are crucial in the first days after discharge. In mild and moderate ambulatory exacerbations, clinical evaluation is required 48–72 h after initiation of therapy. In mild cases, this evaluation can be performed by telephone.

Outcomes of exacerbations: risk factors for failure

The failure rate for ambulatory treatment of exacerbations of COPD ranges from 12% to 26%, and failure may lead to hospital admission. COPD severity is associated with a higher rate of severe exacerbation requiring hospitalisation. The mortality of patients admitted to hospital with a COPD exacerbation is ~10–14%, and the mortality of those admitted to an intensive care unit may be as high as 24%. Hospitalisation has an important impact on COPD patients, being associated with a higher risk of short-term and long-term all-cause mortality at any stage of COPD severity. Frequent exacerbations have been demonstrated to have a negative impact on health-related quality of life in patients with COPD, and survival is significantly related to the frequency and severity of exacerbations. Identification of risk factors for failure of ambulatory treatment indicates the need to implement more aggressive broad-spectrum treatment and closer follow-up.

Prevention of exacerbations of COPD

The prevention of exacerbations of COPD must start with a series of general measures, such as quitting smoking, maintaining or reaching an adequate level of physical activity, and vaccination including the annual anti-influenza and the antipneumococcal vaccines. Pulmonary rehabilitation has also been demonstrated to reduce the risk of exacerbations and hospital stay. Pharmacological treatment should follow some progressive steps, as will be detailed in the next sections. A recent ERS/ATS guideline for the prevention of exacerbations in COPD provides a more comprehensive review of all these treatment alternatives for reducing exacerbations.

First step: optimal bronchodilation

Long-acting bronchodilators are the cornerstone of COPD therapy, and they have also been demonstrated to reduce the frequency of exacerbations. In particular, the long-acting antimuscarinic agents (LAMAs), such as tiotropium, are more effective than long-acting β_2-agonists (LABAs) in the prevention of exacerbations and are preferred as monotherapy in milder patients. If exacerbations persist despite a LAMA, a combination of LAMA/LABA is indicated.

Second step: phenotype-directed treatment

In patients who still suffer exacerbations despite a combination of LAMA/LABA, there are a series of alternatives that can be used, but it is first crucial to check compliance with medication and the adequate use of the inhaler device, and investigate the possible role of comorbidities.

Inhaled corticosteroids are the drugs most widely studied and used for the prevention of exacerbations in COPD. In combination with long-acting bronchodilators, they are particularly effective for the prevention of inflammatory (eosinophilic) exacerbations. Mucolytics and, in particular, high-dose *N*-acetylcysteine or carbocysteine, have been shown to prevent exacerbations, especially in patients with more frequent episodes and more severe COPD. Long-term macrolides, especially azithromycin, are effective in preventing exacerbations in severe COPD patients with frequent bacterial exacerbations despite optimal inhaled therapy. The use of long-term macrolides can be associated with important side-effects and the development of bacterial resistance, and should therefore be restricted to prescription by specialists in reference centres. Roflumilast, a phosphodiesterase-4 inhibitor, is effective in reducing exacerbation frequency in patients with severe COPD and symptoms of chronic bronchitis. However, in some patients the drug must be discontinued due to intolerance to side-effects.

Further reading

- Anthonisen NR, *et al.* (1987). Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med*; 106: 196–204.
- Bafadhel M, *et al.* (2011). Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med*; 184: 662–671.
- Halpin DM, *et al.* (2017). Impact and prevention of severe exacerbations of COPD: a review of the evidence. *Int J Chron Obstruct Pulmon Dis*; 12: 2891–2908.
- Hurst JR, *et al.* (2010). Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*; 363: 1128–1138.
- Llor C, *et al.* (2012). Efficacy of antibiotic therapy for acute exacerbations of mild to moderate chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 186: 716–723.
- Mallia P, *et al.* (2011). Experimental rhinovirus infection as a human model of chronic obstructive pulmonary disease exacerbation. *Am J Respir Crit Care Med*; 183: 734–742.
- Miravitlles M, *et al.* (2013). Antibiotics for acute and chronic respiratory infection in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 188: 1052–1057.
- Miravitlles M, *et al.* (2016). Pharmacological strategies to reduce exacerbation risk in COPD: a narrative review. *Respir Res*; 17: 112.
- Papi A, *et al.* (2006). Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med*; 173: 1114–1121.
- Patel AR, *et al.* (2012). The impact of ischemic heart disease on symptoms, health status, and exacerbations in patients with COPD. *Chest*; 141: 851–857.

- Pavord ID, *et al.* (2016). Blood eosinophils and inhaled corticosteroid/long acting β_2 agonist efficacy in COPD. *Thorax*; 71: 118–125.
- Rothberg MB, *et al.* (2010). Antibiotic therapy and treatment failure in patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease. *JAMA*; 303: 2035–2042.
- Seemungal T, *et al.* (2001). Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 164: 1618–1623.
- Sethi S, *et al.* (2002). New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*; 347: 465–471.
- Stockley RA, *et al.* (2000). Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. *Chest*; 117: 1638–1645.
- Wedzicha JA, *et al.* (2017a). Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*; 49: 1600791.
- Wedzicha JA, *et al.* (2017b). Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*; 50: 1602265.

Extrapulmonary effects of COPD

Yvonne Nussbaumer-Ochsner and Klaus F. Rabe

COPD is an inflammatory disease of the lungs that is characterised by a fixed airflow limitation. Over the past few years, the understanding of COPD has evolved, and it is no longer justified to consider COPD as a disease restricted to the lungs. COPD has become a complex and multicomponent disorder, and the majority of patients die from cardiovascular diseases or cancer and not primarily respiratory diseases. Extrapulmonary comorbidities significantly complicate the management and influence the prognosis of patients with COPD (Mannino *et al.*, 2008). The broad range of clinical presentations ranging from chronic bronchitis to hyperinflation and severe emphysema also illustrates that the term COPD describes patients with very different clinical phenotypes.

There are a number of known extrapulmonary comorbidities of COPD (table 1). In particular, there is large evidence that supports the coexistence of COPD and cardiovascular disease (Chen *et al.*, 2015). While some of these comorbidities share risk factors with COPD, such as cigarette smoking, other frequently observed comorbidities cannot be attributed to smoking. There is increasing evidence that chronic inflammation is a key factor in COPD and is present in many other chronic diseases associated with COPD. The theory that COPD could be considered part of a "chronic systemic inflammatory syndrome" takes these different aspects into account (Fabbri *et al.*, 2007).

Key points

- There is clear evidence that COPD has evolved from a disease limited to the airways to a complex and multicomponent syndrome.
- FEV_1 is not just a lung function parameter for grading COPD severity, but is also a marker for premature death from any cause.
- The course of the disease and the prognosis is influenced by extrapulmonary pathology and accompanying comorbidities.
- Patients with COPD show comorbidities that are not only related to smoking but also to other lifestyle factors including diet and inactivity; chronic systemic inflammation seems to link them together and might explain why they often occur together. These comorbidities should be treated according to common guidelines irrespective of the presence of COPD.
- Future research has to answer the question whether the successful treatment of comorbidities associated with COPD positively influences the course of the disease itself.

Table 1. Systemic manifestations and comorbidities of COPD

Cardiovascular diseases
Ischaemic heart disease
Hypertension
Pulmonary hypertension
Congestive heart failure
'Metabolic' disorders
Osteoporosis
Skeletal muscle weakness
Cachexia: weight loss and muscle wasting
Diabetes mellitus
Metabolic syndrome
Other comorbid diseases
Lung cancer
Chronic kidney disease
Depression
Obstructive sleep apnoea syndrome
Normocytic anaemia

Local and systemic inflammation

In industrialised countries of the western world, cigarette smoking accounts for most cases of COPD. Smoking triggers a local inflammatory response throughout the whole tracheobronchial tree. The cellular pattern is quite heterogenous and inflammatory cells are found in the proximal and peripheral small airways, the lung parenchyma and the pulmonary vasculature. Apart from these local effects, smoking may significantly contribute to or cause systemic inflammation. COPD patients show endothelial dysfunction irrespective of cardiovascular risk factors indicating that airflow obstruction and systemic inflammation may increase the risk of cardiovascular disease in patients with COPD (Eickhoff *et al.*, 2008). COPD patients suffering from an acute exacerbation or having severe disease stage show increased markers of interleukins (IL)-6, IL-8 and tumour necrosis factor (TNF)-α, acute-phase proteins (C-reactive protein and fibrinogen) and circulating inflammatory cells (monocytes, neutrophils and lymphocytes) (Barnes *et al.*, 2009). Whether this systemic inflammation is the result of a "spill-over" of local inflammation in the lungs, a systemic inflammatory effect that affects multiple organ systems, or is attributable to some comorbid conditions that affect the lungs, remains debatable (figure 1).

Systemic inflammation is actually not only present in patients with COPD, but is also a common feature in various other chronic diseases. Compared to healthy individuals, elevated levels of inflammatory markers such as C-reactive protein and IL-6 are observed in patients with stable coronary artery disease, peripheral arterial disease and diabetes (Wisniacki *et al.*, 2005; Nijm *et al.*, 2005). These findings have to be taken into account when the causative role of COPD in systemic inflammation is investigated because these conditions often occur together. Systemic inflammation might be the common pathway leading to these chronic diseases and might explain the high prevalence of multiple chronic diseases in the same patient.

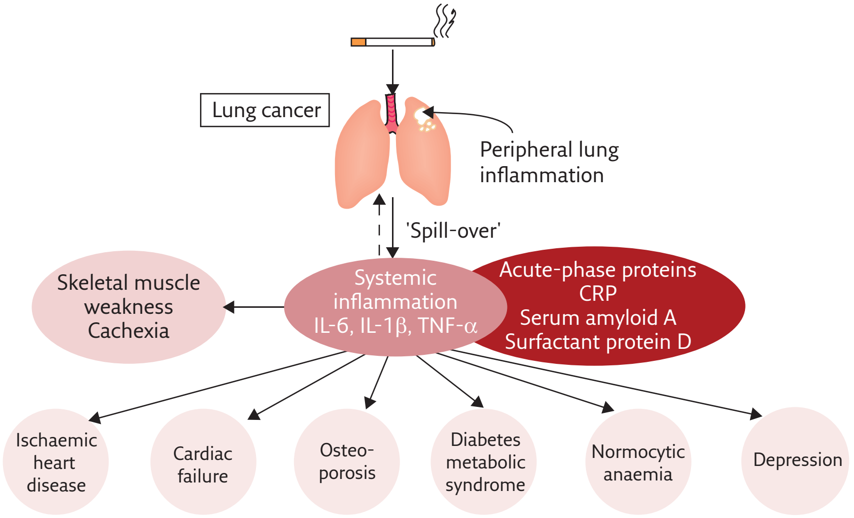

Lung cancer
Peripheral lung inflammation
'Spill-over'
Skeletal muscle weakness Cachexia
Systemic inflammation IL-6, IL-1β, TNF-α
Acute-phase proteins CRP Serum amyloid A Surfactant protein D
Ischaemic heart disease
Cardiac failure
Osteo-porosis
Diabetes metabolic syndrome
Normocytic anaemia
Depression

Figure 1. Systemic effects and comorbidities of COPD. Peripheral lung inflammation may cause a "spill-over" of cytokines, such as IL-6, IL-1β and TNF-α, into the systemic circulation, which may increase acute-phase proteins such as C-reactive protein (CRP). Systemic inflammation may then lead to skeletal muscle atrophy and cachexia and may initiate and worsen comorbid conditions. Systemic inflammation may also accelerate lung cancer. An alternative model is that systemic inflammation causes several inflammatory diseases, including COPD. Reproduced from Barnes et al. *(2009).*

Impact on patient care

Comorbidities and systemic effects in patients with COPD not only have prognostic value but also result in implications for medical treatment. Medical care should focus on comorbidities that are easier to prevent and treat than COPD itself. A diagnosis of COPD can easily be performed by spirometry but the severity of the disease is clearly dependent on the presence of comorbidities. Therefore, it has been propagated that any patient aged >40 years with a positive smoking history (>10 pack-years), symptoms and a lung function compatible with COPD should be carefully evaluated for more general disorders associated with the chronic systemic inflammatory syndrome (table 2) (Fabbri *et al.*, 2007).

Therapeutic implications

Pharmacological treatment targeting the lungs has only a minor impact on the course of the disease, and the treatment of COPD should no longer be centred

Table 2. Components of the chronic systemic inflammatory syndrome

Age >40 years
Smoking for >10 pack-years
Symptoms and lung function compatible with COPD
Chronic heart failure
Metabolic syndrome
Increased C-reactive protein
At least three components are required for diagnosis. Reproduced from Fabbri *et al.* (2007).

just on controlling symptoms and reducing exacerbations. Large clinical trials have shown that available drugs for COPD (bronchodilators, inhaled corticosteroids) do not significantly influence the long-term decline in FEV_1. Another approach would be to target the underlying systemic disease itself and to look beyond the lungs for drugs to treat patients with COPD. Such classes of drugs encompass statins, β-blockers and anti-platelets. The effect of statins in COPD is not yet fully clear. While simvastatin had no effect on exacerbation rate in a prospective, randomised, placebo-controlled trial (Criner *et al.*, 2014), a meta-analysis found a positive effect with respect to improving exercise tolerance and pulmonary function. These findings need to be confirmed by randomised controlled trials specifically designed to test this hypothesis and identify appropriate patients for statin use (Zhang *et al.*, 2017). Retrospective studies suggest a benefit of β-blockers on mortality in COPD patients. A randomised controlled study for the use of β-blockers for the prevention of acute exacerbation of COPD is ongoing (clinicaltrials.gov NCT02587351). Another class are anti-platelets. Platelet activation has been shown to be increased in patients with stable COPD and during an acute exacerbation. Anti-platelet drugs have been shown to improve survival in patients very severe oxygen-dependent COPD (Ekstrom *et al.*, 2013) and in patients following hospital admittance for an acute exacerbation (Harrison *et al.*, 2014). Furthermore, a meta-analysis suggests anti-platelet therapy reduces all-cause mortality in COPD patients independent of the presence ischaemic heart disease (Pavasini *et al.*, 2016). However, these findings have to be confirmed in prospective and carefully controlled trials before any conclusion about the management in COPD patients can be drawn. Assuming systemic inflammation as the key factor in COPD and other chronic diseases, pulmonary rehabilitation addresses important extrapulmonary components which are not targeted by any pharmacological treatment and might be the reason of its overwhelming efficacy. Lifestyle interventions in general and pulmonary rehabilitation specifically are essential components of patient care and should be evaluated in any COPD patient with Global Initiative for Chronic Obstructive Lung Disease stage II or higher. Appropriate education about the disease itself, its time course and treatment options as well as psychosocial support including smoking cessation and nutritional interventions are part of a successful rehabilitation programme.

Conclusions

Chronic diseases, including COPD, share common aspects, and chronic systemic inflammation seems to be one of the linking elements. Extrapulmonary effects of COPD not only influence the prognosis but also have an impact on disease management. The treatment of patients with COPD must become truly multidisciplinary and has to move from an organ-specific to a more holistic approach.

Further reading

- Barnes PJ, *et al.* (2009). Systemic manifestations and comorbidities of COPD. *Eur Respir J*; 33: 1165–1185.
- Chen W, *et al.* (2015). Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease; a systematic review and meta-analysis. *Lancet Respir Med*; 3: 631–639.
- Criner GJ, *et al.* (2014). Simvastatin for the prevention of exacerbations in moderate-to-severe. *COPD*; 370: 2201–2210.
- Eickhoff P, *et al.* (2008). Determinants of systemic vascular function in patients with stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 178: 1221–1218.

- Ekstrom MP, *et al.* (2013). Effects of cardiovascular drugs on moratlity in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 187: 715–720.
- Fabbri LM, *et al.* (2007). From COPD to chronic systemic inflammatory syndrome? *Lancet*; 370: 797–799.
- Harrison MT, *et al.* (2014). Thrombocytosis is associated with increased short and long term mortality after exacerbation of chronic obstructive pulmonary disease: a role for antiplatelet therapy? *Thorax*; 69: 609–615.
- Mannino DM, *et al.* (2008). Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J*; 32: 962–969.
- Mortensen EM, *et al.* (2009). Impact of statins and ACE inhibitors on mortality after COPD exacerbations. *Respir Res*; 10: 45.
- Nijm J, *et al.* (2005). Circulating levels of proinflammatory cytokines and neutrophil-platelet aggregates in patients with coronary artery disease. *Am J Cardiol*; 95: 452–456.
- Nussbaumer-Ochsner Y, *et al.* (2011). Systemic manifestations of COPD. *Chest*; 139: 165–173.
- Pavasini R, *et al.* (2016). Antiplatelet treatment reduces all-cause mortality in COPD patients: a systematic review and meta-analysis. *COPD*; 13: 509–514.
- Wisniacki N, *et al.* (2005). Insulin resistance and inflammatory activation in older patients with systolic and diastolic heart failure. *Heart*; 91: 32–37.
- Young RP, *et al.* (2007). Forced expiratory volume in one second: not just a lung function test but a marker of premature death from all causes. *Eur Respir J*; 30: 616–622.
- Zhang W, *et al.* (2017). Effect of statins on COPD: a meta-analysis of randomized controlled trials. *Chest*; 15: 1159–1168.

Pharmacology of asthma and COPD

Peter J. Barnes

The pharmacology of asthma and COPD involves understanding the mechanisms and clinical use of bronchodilators and controller therapies.

- Relievers (bronchodilators) give immediate reversal of airway obstruction, largely by relaxing airway smooth muscle.
- Controllers (preventers) suppress the underlying disease process (anti-inflammatory treatments) and provide long-term control of symptoms.
- The most effective therapies are given by inhalation to reduce side-effects.

β_2-adrenergic agonists

Inhaled β_2-agonists are the bronchodilator treatment of choice in asthma because they reverse all known bronchoconstrictor mechanisms and have minimal side-effects when used correctly.

Mode of action

- β_2-agonists produce bronchodilatation by directly stimulating β_2-receptors in airway smooth muscle, leading to dilatation of central and peripheral airways. β_2-agonists are functional antagonists as they reverse bronchoconstriction irrespective of the contractile agent. This is important in asthma, as many bronchoconstrictor

Key points

- Long-acting β_2-agonists are effective as add-on therapy to inhaled corticosteroids in asthma and for reducing symptoms in COPD, and act as functional antagonists.
- Inhaled corticosteroids are the mainstay of asthma control and suppress activated inflammatory genes, but are largely ineffective in COPD (corticosteroid resistance).
- Long-acting muscarinic antagonists are effective bronchodilators in COPD where cholinergic tone is the only reversible component.
- Low-dose theophylline may be useful as an add-on therapy in severe asthma and COPD and may reduce corticosteroid resistance.
- For patients with very severe asthma not controlled on maximal inhaled therapy consider biological therapy with anti-IgE if allergic or anti-interleukin (IL)-5 if eosinophilic.

mechanisms (neural and mediators) contribute, whereas in COPD, their major effect is to reverse cholinergic tone. Stimulation of β$_2$-receptors results in the activation of adenylyl cyclase *via* the stimulatory G-protein (G_s), which increases intracellular cyclic AMP, leading to relaxation of myosin fibrils. β$_2$-receptors are localised to several types of airway cell and β$_2$-agonists may have additional effects.

- In addition to direct relaxation of airway smooth muscle, β$_2$-agonists may also have beneficial effects by inhibiting the release of mediators from mast cells and of neurotransmitters from airway nerves, as well as reducing plasma exudation from airway blood vessels.
- However, β$_2$-agonists have no significant long-term effects on chronic inflammation of the airways so in asthma patients they need to be used with a controller therapy.

Short-acting inhaled β$_2$-agonists

Short-acting inhaled β$_2$-agonists (SABAs) (*e.g.* salbutamol and terbutaline) bronchodilate for 4–6 h (less in severe asthma) and are used mainly by inhalation as reliever therapy in asthma and COPD. They have a rapid onset and are without significant side-effects. They also protect against bronchoconstrictor stimuli such as exercise, cold air and allergens. SABAs are the bronchodilators of choice in acute severe asthma and COPD, in which the nebulised route of administration is as effective as *i.v.* use. Inhaled delivery is preferable to oral delivery because side-effects are less common and it may be more effective (better access to surface cells such as mast cells). They should not be used on a regular basis; increased use indicates a need for more anti-inflammatory therapy.

Long-acting inhaled β$_2$-agonists

Long-acting inhaled β$_2$-agonists (LABAs) include salmeterol and formoterol twice daily, and indacaterol, vilanterol, olodaterol once daily. These drugs have a prolonged bronchodilator and bronchoprotective action. Formoterol has a more rapid onset of action but is a fuller agonist than salmeterol, so tolerance is more likely. Formoterol, but not salmeterol, is more effective as a reliever than SABAs. Inhaled LABAs are added to low or moderate doses of inhaled corticosteroids (ICS) and this is more effective than increasing the dose of ICS, but LABAs should never be used without an ICS in asthma. Combination inhalers with an ICS and a LABA (*e.g.* fluticasone propionate/salmeterol, budesonide/formoterol, beclomethasone dipropionate/formoterol, and fluticasone furoate/vilanterol) are an effective and convenient way to control asthma and are also useful in COPD. Budesonide/formoterol is very effective as a reliever when added to maintenance treatment with the same drug and is more effective than a SABA as a reliever in mild asthma. LABAs are effective bronchodilators in COPD and reduce exacerbations. Indacaterol and olodaterol have a duration of action >24 h and are approved as a once daily treatment for COPD patients.

Side-effects

Unwanted effects result from stimulation of extrapulmonary β-receptors and include muscle tremor, palpitations, restlessness and hypokalaemia. Side-effects are relatively uncommon with inhaled therapy, but more common with oral or *i.v.* administration.

Safety

A large trial in the USA showed that salmeterol increased mortality and near-death asthma attacks in asthmatic patients, but this was mainly in poor patients who were not using concomitant ICS. This provides a strong argument for prescribing LABAs only in a combination inhaler. Recent safety trials of ICS-LABA in asthma showed no evidence for increased mortality. There are no safety concerns about LABA use in COPD.

Tolerance

Loss of bronchodilator action is minimal, but there is some loss of the bronchoprotective effect against exercise, for example. This is incomplete and progressive only for a few days, it does not appear to be a clinical problem.

Anticholinergics

Atropine is a naturally occurring compound that was introduced for the treatment of asthma but, because of side-effects (particularly drying of secretions and hallucinations), less soluble quaternary compounds (*e.g.* ipratropium bromide) were developed.

Mode of action

Anticholinergics are specific antagonists of muscarinic receptors and block cholinergic nerve-induced bronchoconstriction. A small degree of resting bronchomotor tone is present because of tonic cholinergic nerve impulses, which release acetylcholine in the vicinity of airway smooth muscle, and cholinergic reflex bronchoconstriction may be initiated by irritants, cold air and stress. Although anticholinergics protect against acute challenge by sulphur dioxide and emotional factors, they are less effective against allergens, exercise and fog. They inhibit reflex cholinergic bronchoconstriction only and have no significant blocking effect on the direct effects of inflammatory mediators, such as histamine and leukotrienes. In COPD, cholinergic tone is the only reversible element of airway narrowing as anticholinergics are as effective as β_2-agonists.

Clinical use

Ipratropium bromide and oxitropium bromide are inhaled three or four times daily, whereas long-acting muscarinic antagonists (LAMA) are inhaled once or twice daily. In asthmatic patients, anticholinergic drugs are less effective bronchodilators than β_2-agonists and offer less protection against bronchial challenges. Nebulised anticholinergics are effective in acute severe asthma, but less effective than β_2-agonists, so may be added if responses to nebulised β_2-agonists are insufficient. Recent studies have demonstrated that tiotropium may be an effective add-on bronchodilator in some patients with severe asthma and in patients with asthma–COPD overlap (ACO) features. Inhaled LAMA are the bronchodilators of choice in COPD and reduce symptoms. Tiotropium and umeclidinium are effective once daily, aclidinium twice daily and glycopyrrolate once or twice daily depending on the dose. LABA and LAMA have additive bronchodilator effects in COPD, with greater reduction of symptoms and exacerbation than either drug alone. Several fixed dose combination LABA-LAMA inhalers are now available for COPD. Patients with ACO and some patients with COPD (frequent exacerbators with increased blood eosinophils) may benefit from a fixed dose triple combination of ICS-LABA-LAMA.

Side-effects

Inhaled anticholinergic drugs are well tolerated, and systemic side-effects are uncommon because very little systemic absorption occurs. Ipratropium bromide, even in high doses, has no detectable effect on airway secretions. Nebulised ipratropium bromide may precipitate glaucoma in elderly patients as a result of a direct effect of the nebulised drug on the eye; this is avoided by use of a mouthpiece rather than a facemask. Dry mouth occurs in about 10% of patients on LAMA but rarely requires discontinuation of treatment. Urinary retention and glaucoma are very rare adverse effects.

Theophylline

Theophylline remains the most widely used asthma therapy worldwide because it is inexpensive, but the greater incidence of side-effects with theophylline and the greater efficacy of β_2-agonists and ICS have reduced its use. It remains a useful third-line drug in patients with severe asthma and COPD.

Mode of action

Theophylline is a weak, nonselective phosphodiesterase (PDE) inhibitor, which causes bronchodilatation by inhibiting PDE3 in airway smooth muscle at concentrations $>10\ \text{mg}\cdot\text{L}^{-1}$. At these concentrations, it is also an antagonist of adenosine receptors and inhibition of A_{2B}-receptors on mast cells could contribute to its beneficial effect in asthma, but blockage of A_1-receptors may lead to serious side-effects, such as cardiac arrhythmias and seizures. At lower concentrations ($5–10\ \text{mg}\cdot\text{L}^{-1}$) theophylline may have anti-inflammatory effects in asthma and COPD, either through PDE4 inhibition or, more likely, through inhibition of phosphoinositide-3-kinase-δ. This may also explain how theophylline can reverse corticosteroid resistance in asthma and COPD by increasing histone deacetylase (HDAC)2 activity to allow corticosteroids to switch off activated inflammatory genes.

Clinical use

i.v. aminophylline (a stable mixture or combination of theophylline and ethylenediamine that confers greater solubility in water) is less effective than nebulised β_2-agonists in the treatment of acute severe asthma, and should therefore be reserved for the few patients who fail to respond to β_2-agonists. Theophylline is less effective as a bronchodilator than inhaled β_2-agonists and is more likely to have side-effects. There is increasing evidence that low doses (giving plasma concentrations of $5–10\ \text{mg}\cdot\text{L}^{-1}$) may be useful when added to ICS, particularly in more severe asthma and in COPD, reducing hyperinflation and improving dyspnoea.

Pharmacokinetics

Theophylline is reliably absorbed from the gastrointestinal tract, but many factors affect plasma clearance and, thus, plasma concentration. Clearance may be increased by drugs that induce hepatic cytochrome P450, mainly the CYP1A2 isoenzyme (*e.g.* rifampicin and ethanol), by smoking and in children, so higher doses may be needed. Clearance is reduced by drugs that inhibit hepatic metabolism (*e.g.* cimetidine, erythromycin and ciprofloxacin), congestive cardiac failure, liver disease, viral infections, and in the elderly.

Side-effects

These are related to plasma concentration and tend to occur when plasma levels exceed $20\ \text{mg}\cdot\text{L}^{-1}$, although some patients develop them at lower plasma concentrations. The severity of side-effects may be reduced by gradually increasing the dose until therapeutic concentrations are achieved. The most common side-effects are headache, nausea and vomiting, and abdominal discomfort (probably due to PDE4 inhibition), while the dangerous side-effects are cardiac arrhythmias and seizures (due to A_1-receptor antagonism).

Corticosteroids

Corticosteroids are the most effective controller therapy available for asthma, but are poorly effective in most patients with COPD.

Mode of action

Corticosteroids enter target cells and bind to glucocorticoid receptors in the cytoplasm. The corticosteroid–receptor complex is transported to the nucleus, where it binds to specific sequences on the upstream regulatory element of responsive target genes, resulting in increased or decreased transcription and, subsequently, increased or decreased protein synthesis. Glucocorticoid receptors may also inhibit transcription factors, such as nuclear factor (NF)-κB, which activate inflammatory gene expression by a nongenomic mechanism. Corticosteroids inhibit histone acetylation and, thereby, inflammatory gene expression by recruiting HDAC2 to the transcriptional complex. The mechanism of action of corticosteroids in asthma is mostly related to their anti-inflammatory effects and, particularly, suppression of transcription of activated inflammatory genes (*e.g.* cytokines). They also have inhibitory effects on many inflammatory and structural cells that are activated in asthma, resulting in reduced airway hyperresponsiveness. By contrast, corticosteroids have no anti-inflammatory effects in most patients with COPD and reduced benefit in severe asthma, which may be explained by a reduction in HDAC2 activity as a consequence of oxidative stress.

Clinical use

Systemic corticosteroids are used in acute exacerbations of asthma and accelerate their resolution. There is no advantage with high doses of *i.v.* corticosteroids (*e.g.* methylprednisolone, 1 g). Prednisolone (40–60 mg orally) has an effect similar to *i.v.* hydrocortisone and is easier to administer. Maintenance oral corticosteroids are reserved for patients whose asthma cannot be controlled by other therapies (Global Initiative for Asthma (GINA) step 5); the dose is titrated to the lowest that provides acceptable symptom control. Short courses of oral corticosteroids (prednisolone, 30–40 mg daily for 5–14 days) are indicated for exacerbations of asthma; the dose may be tapered over 1 week once the exacerbation is resolved.

ICS are currently recommended as first-line therapy in all patients with persistent asthma and may be started in any patient who needs to use a SABA inhaler for symptom control more than once a week. In most patients, ICS are used twice daily, but once daily use may be possible in patients with mild asthma. If a dose of >800 µg daily *via* a metered-dose inhaler is administered, a spacer should be used to reduce the risk of oropharyngeal side-effects and of absorption from the gastrointestinal tract. ICS in doses of ≤400 µg daily may be used safely in children. Patients with COPD show a poor response to ICS with no effect on disease progression or mortality, but ICS reduce exacerbations in patients who have severe disease and frequent exacerbations. However, in COPD patients with increased blood eosinophils (>300 cells $\cdot$ µL^{-1}) and ≥2 exacerbations per year ICS are more effective in preventing exacerbations.

Side-effects

Corticosteroids inhibit cortisol secretion by a negative feedback effect on the pituitary gland. Hypothalamic–pituitary–adrenal axis suppression is dependent on dose and usually occurs when an oral dose of prednisolone of more than 7.5–10 mg daily is used. Significant suppression after short courses of corticosteroid therapy is not usually a problem, but prolonged suppression may occur after several months or years; therefore, corticosteroid doses must be reduced slowly after prolonged oral therapy. Symptoms of 'corticosteroid withdrawal syndrome' include lassitude, musculoskeletal pains and occasionally fever.

Side-effects of long-term oral corticosteroid therapy include fluid retention, increased appetite, weight gain, osteoporosis, capillary fragility, hypertension, peptic ulceration, diabetes, cataracts and psychosis. The incidence tends to increase with age.

Systemic side-effects of ICS have been investigated extensively. Effects such as cataract formation and osteoporosis are reported, but often in patients who are also receiving courses of oral corticosteroids. There has been particular concern about growth suppression in children using ICS but, in most studies, doses of ≤400 μg have not been associated with impaired growth and there may even be a growth spurt because asthma is better controlled. In COPD patients, high doses of ICS have been associated with cataracts, fractures, type 2 diabetes and pneumonia.

The fraction of corticosteroid inhaled into the lungs acts locally on the airway mucosa and may be absorbed from the airway and alveolar surface, thereby reaching the systemic circulation. The fraction of ICS deposited in the oropharynx is swallowed and absorbed from the gut, and is then metabolised in the liver before it reaches the systemic circulation. Budesonide and fluticasone propionate have a greater first-pass metabolism than beclomethasone dipropionate and are therefore less likely to produce systemic effects at high inhaled doses. The use of a spacer reduces oropharyngeal deposition, thereby reducing systemic absorption of corticosteroid.

Antileukotrienes

Antileukotrienes (leukotriene receptor antagonists) are much less effective than ICS in the control of asthma.

Mode of action

Elevated concentrations of leukotrienes are detectable in bronchoalveolar lavage fluid and sputum of asthmatic patients. Cysteinyl-leukotrienes (Cys-LTs) are generated from arachidonic acid by the rate-limiting enzyme 5-lipoxygenase. Cys-LTs are potent constrictors of human airways *in vitro* and *in viv*o, cause airway microvascular leakage in animals, and stimulate airway mucus secretion. These effects are all mediated in human airways *via* Cys-LT_1 receptors. Montelukast and zafirlukast are potent Cys-LT_1 receptor antagonists that markedly inhibit the bronchoconstrictor response to inhaled leukotrienes, reduce allergen-, exercise- and cold air-induced asthma by about 50–70%, and inhibit acute aspirin-induced responses in aspirin-sensitive asthmatic patients almost completely. They may also have weak anti-inflammatory effects and may reduce eosinophilic inflammation.

Clinical use

Antileukotrienes may have a small and variable bronchodilator effect, indicating that leukotrienes may contribute to baseline bronchoconstriction in asthma. Long-term administration reduces asthma symptoms and the need for rescue β_2-agonists, and improves lung function. However, their effects are significantly less than with ICS in terms of symptom control, improvement in lung function and reduction in exacerbations. They may be useful in some patients whose asthma is not controlled on ICS as an add-on therapy, but are less effective in this respect than LABAs or low dose theophylline. They are effective in some, but not all, patients with aspirin-sensitive asthma and are less effective than ICS. Patients appear to differ in their response to antileukotrienes, and it is impossible to predict which patients will respond best. A major advantage is that they are orally active and may improve compliance with long-term therapy.

Side-effects

Antileukotrienes are well tolerated and there are no class-specific side-effects. Zafirlukast may produce mild liver dysfunction, so liver function tests are important. Several cases of eosinophilic granulomatosis with polyangiitis (systemic vasculitis with eosinophilia and asthma) have been observed in patients on antileukotrienes, but these may be because a concomitant reduction in oral corticosteroids (made possible by the antileukotriene) allows the vasculitis to flare up.

Anti-IgE

Mode of action

Omalizumab is a humanised recombinant monoclonal antibody that binds to circulating IgE and, thus, blocks it from activating high-affinity IgE receptors on mast cells and low-affinity IgE receptors on other inflammatory cells, resulting in reduced responses to allergens. Over time, the blocking of IgE reduces its synthesis by B-cells and results in a sustained reduction in free IgE.

Clinical use

Omalizumab reduces airway inflammation in patients with mild-to-moderate asthma and reduces the incidence of asthma exacerbations, with improved control of asthma in patients maintained on reduced doses of ICS or oral steroids. Omalizumab is most useful in patients with severe asthma who are not controlled on maximal doses of inhaled therapy as it reduces exacerbations and improves asthma control. Only ~30% of patients show a good response and this is not predicted by any clinical features; therefore, a trial of therapy over 4 months is indicated. Omalizumab should be given only to patients with serum IgE levels of 20–1500 $\text{IU} \cdot \text{mL}^{-1}$; above these levels, it is not possible to give enough antibody to neutralise the IgE. The dose of omalizumab is determined by serum IgE levels and body weight, and it is given either once or twice a month. Because of its high cost, only patients at GINA steps 4 and 5 with frequent exacerbations are suitable for this therapy.

Side-effects

Occasionally, local reactions occur at the injection sites and, very rarely, anaphylactic reactions have been reported.

Anti-IL-5

IL-5 plays an essential role in the generation of eosinophils from the bone marrow and in mediating type 2 immunity in asthma. Blocking antibodies to IL-5 (mepolizumab, reslizumab) or its receptor IL-5Rα (benralizumab) markedly reduce blood and airway eosinophils in asthma. In patients with severe asthma and persistent eosinophils (blood eosinophils >300 $\text{cells} \cdot \mu\text{L}^{-1}$) despite maximal ICS, anti-IL-5 treatments reduce exacerbations by ~50% and the need for oral corticosteroid maintenance treatment, although there is only a small effect on symptoms, lung function or quality of life. These treatments may be indicated in severe eosinophilic asthma that is uncontrolled with maximal inhaler therapy. In eosinophilic COPD anti-IL-5 therapy has little effect in reducing exacerbations.

Roflumilast

Roflumilast is a once daily oral PDE4 inhibitor that has anti-inflammatory effects in COPD patients. Roflumilast is a pro-drug that is converted in the liver to its active long-lasting metabolite roflumilast-*N*-oxide. In COPD patients with severe disease (FEV_1 <50% predicted), chronic bronchitis and frequent exacerbations (≥2 per year), there is a small improvement in lung function and a reduction in severe exacerbations. It is therefore used as an add-on therapy in this subpopulation of patients with COPD already on triple therapy.

Side effects

The dose is limited by the side-effects (nausea, vomiting, diarrhoea and headaches), which are also due to PDE4 inhibition, so its clinical efficacy is relatively small. Weight loss may also occur, but this is nonprogressive and reversible. Roflumilast should never be co-administered with theophylline, which also inhibits PDE4.

Macrolides

Macrolide antibiotics, such as azithromycin, reduce exacerbations in COPD patients on triple therapy, but it is not certain whether this is due to their antibiotic effects or an anti-inflammatory action that inhibits NF-κB. A macrolide may be added to triple therapy to reduce exacerbations and are more effective in ex-smokers than current smokers.

Side effects

Side effects include deafness, cardiac arrhythmias, diarrhoea and development of antibiotic resistance.

Immunosuppressive/corticosteroid-sparing therapy

Immunosuppressive therapy has been considered in asthma when other treatments have been unsuccessful or when a reduction in the dosage of oral corticosteroids is required; it is therefore indicated in very few (<1%) asthmatic patients at present.

Methotrexate

Low-dose methotrexate (15 mg weekly) has a corticosteroid-sparing effect in some patients with asthma, but side-effects are relatively common and include nausea (reduced if methotrexate is given as a weekly injection), blood dyscrasia and hepatic damage. Careful monitoring (monthly blood counts and liver enzymes) is essential.

Cyclosporin A

Low-dose oral cyclosporin A in patients with corticosteroid-dependent asthma is reported to improve control of symptoms but, in clinical practice, it is unimpressive and its use is limited by severe side-effects (nephrotoxicity and hypertension).

Further reading

- Barnes PJ (2017). Pulmonary pharmacology. *In*: Brunton LL, ed. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 13th Edn. New York, McGraw Hill, 2017; pp. 727–750.
- Barnes PJ (2018). Targeting cytokines to treat asthma and chronic obstructive pulmonary disease. *Nat Rev Immunol* 2018; 18: 454–466.
- Barnes PJ, *et al*. (2015). Chronic obstructive pulmonary disease. *Nature Rev Primers* 2015; 1: 115076–21.

- Global Initiative for Asthma (2018). Global strategy for asthma management and prevention. https://ginasthma.org/gina-reports
- Global Initiative for Chronic Obstructive Lung Disease (2018). Global strategy for the diagnosis, management and prevention of COPD. https://goldcopd.org/gold-reports/2018
- Israel E, *et al*. (2017). Severe and difficult-to-treat asthma in adults. *N Engl J Med*; 2017; 377: 965–76976.

Bronchiectasis

James D. Chalmers

Bronchiectasis is a disorder characterised by abnormal dilatation of the bronchi and a clinical syndrome of cough, sputum production and recurrent respiratory tract infections. Fatigue, breathlessness, haemoptysis and chest discomfort are also relatively common symptoms.

Pathophysiology is defined by a vicious 'vortex' consisting of a combination of neutrophil mediated inflammation, chronic infection with bacteria, structural lung damage and impaired mucociliary clearance. The prevalence has increased at least 40% in the past 10 years and the disease is more common with increasing age and is more common in females.

Presentation and diagnosis

Bronchiectasis should be suspected in patients with chronic cough particularly when accompanied by mucopurulent or purulent sputum production. Patients with recurrent respiratory tract infections should also be considered. The disease may present at any age from early childhood to the very elderly. Many patients have a past history of asthma or COPD. Bronchiectasis should be considered in these disorders where management is not straightforward, where there is frequent isolation of pathogenic bacteria or where sputum production is a prominent feature.

Key points

- Bronchiectasis should be suspected in patients with chronic productive cough and/or recurrent respiratory tract infections. A HRCT scan is the most useful diagnostic test.
- A diagnosis of bronchiectasis should prompt a search for the underlying cause; treatable underlying causes such as allergic bronchopulmonary aspergillosis, immunodeficiency and non-tuberculous mycobacterial infection should be excluded at diagnosis.
- Regular sputum samples are helpful to guide treatment both in terms of selecting antibiotics for treatment of exacerbations and detecting bacteria such as *Pseudomonas aeruginosa* which have prognostic implications.
- Airway clearance and prompt treatment of exacerbations with antibiotics are the mainstay of treatment. Patients with frequent exacerbations are at higher risk of long-term morbidity and mortality and so should be considered for additional treatment, such as prophylactic antibiotics or mucoactive drugs.

Spirometry in bronchiectasis may be obstructive but normal spirometry or a restrictive pattern are also commonly seen.

HRCT scanning is the most appropriate diagnostic test when bronchiectasis is suspected. Chest radiography is insufficiently sensitive to exclude the diagnosis. The diagnostic feature is an increase in the ratio between the bronchial diameter and the adjacent vascular diameter (called the bronchoarterial ratio). At any point the bronchoarterial ratio is normally <1. A bronchoarterial ratio >1 is diagnostic of radiological bronchiectasis. Additional criteria are a lack of normal tapering and visualisation of the bronchi within 1 cm of the pleural surface. Bronchial wall thickening is also supportive of the diagnosis but can be seen in other conditions not associated with bronchiectasis. Mucus plugging is also a commonly observed feature (figure 1).

Different radiological subtypes of bronchiectasis are shown in figure 1 and include: 1) tubular bronchiectasis in the lower lobes; 2) varicose bronchiectasis in lower lobes; 3) CF in the right lower lobe; 4) cystic bronchiectasis with tree-in-bud pattern and mucus plugging in the lower lobes, plus cavitation in the right lower lobe; 5) extensive mucus plugging in the lower lobes; and 6) varicose bronchiectasis in the upper lobes and lingula (Contarini *et al.*, 2018).

Diagnostic testing

The critical first step following a diagnosis of bronchiectasis is to determine the underlying cause. This is possible in 30–60% of cases with the rest of cases classified as idiopathic. The European Respiratory Society (ERS) guidelines recommend initial

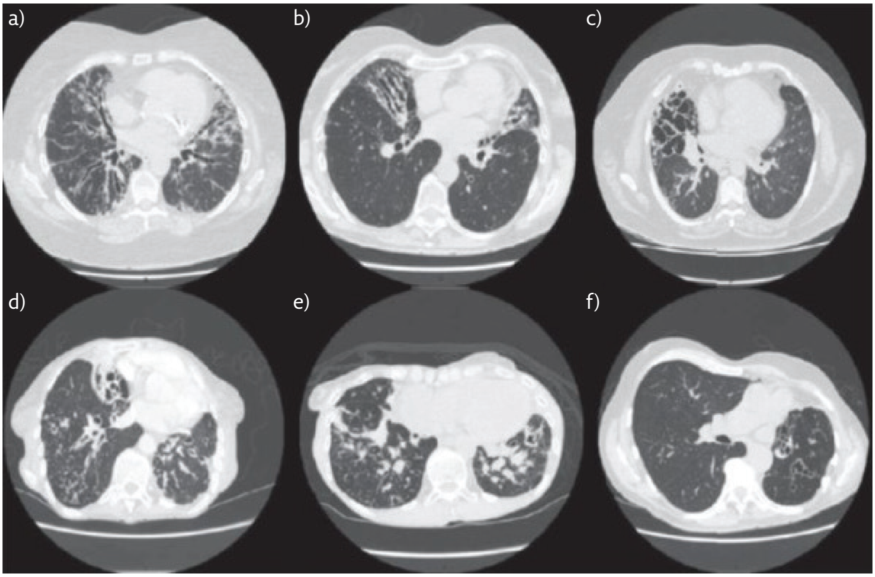


Figure 1. Different radiological subtypes of bronchiectasis. a) Tubular bronchiectasis in the lower lobes, b) varicose bronchiectasis in lower lobes, c) CF in the right lower lobe, d) cystic bronchiectasis with tree-in-bud pattern and mucus plugging in the lower lobes, plus cavitation in the right lower lobe, e) extensive mucus plugging in the lower lobes, f) varicose bronchiectasis in the upper lobes and lingula. Reproduced from Contarini et al. *(2018) with permission.*

screening with serum immunoglobulins (IgA, IgG and IgM) and tests for allergic bronchopulmonary aspergillosis (total immunoglobulin (Ig)E and specific IgE to *Aspergillus* along with IgG to *Aspergillus* or *Aspergillus* precipitins). It is also advisable to test for nontuberculous mycobacteria (NTM) by sending sputum for acid-fast bacilli (AFB) testing. Antibody responses to the pneumococcal polysaccharide vaccine can help to identify immunodeficiency. Other tests are guided by the clinical presentation. Some causes of bronchiectasis such as severe infections, TB, inflammatory bowel disease and rheumatoid arthritis (and other connective tissue diseases, *e.g.* Sjögrens syndrome) may be evident from history and physical examination. Others require additional testing to confirm. Some patients are still diagnosed with CF in adulthood and this should be suspected in the presence of upper lobe disease, isolation of *Staphylococcus aureus* or *Pseudomonas aeruginosa* and non-pulmonary manifestations suggestive of CF (pancreatitis, infertility and malabsorption). Primary ciliary dyskinesia (PCD) can be associated with rhinosinusitis, onset of symptoms during childhood, dextrocardia and a history of middle ear infections. Unlike CF, PCD tends to affect the middle and lower lobes. α_1-antitrypsin deficiency can be a cause of bronchiectasis and may be associated with basal emphysema. Testing for CF requires a sweat test and genetics, while low nasal nitric oxide can be used as a screening test for PCD, followed by additional diagnostic tests that are best performed in a specialist centre, such as high-speed video microscopy, electron microscopy and/or genetics.

Microbiology

Across Europe the most frequently isolated organisms are the Gram-negative organisms *P. aeruginosa* and *Haemophilus influenzae. P. aeruginosa* is the most frequent organism in severe bronchiectasis and is associated with a 7-fold increased risk of hospital admission and 3-fold increased risk of death compared to other pathogens. Less frequent organisms include enterobacteriaceae (*Escherichia coli, Klebsiella pneumoniae*), *S. aureus*, *Moraxella catarrhalis* and NTM (most frequently *Mycobacterium avium* complex and *Mycobacterium abscessus* complex). NTM should be actively sought by performing staining for AFB and mycobacterial culture. Most international guidelines suggest that a sputum culture should be sent at each clinical encounter and at least once per year.

Management of stable patients

The objective of treatment is to reduce symptoms, prevent exacerbations, improve quality of life and where possible prevent disease progression and mortality. The evidence base for most bronchiectasis therapies is weak. Treatment of the underlying cause such as Ig replacement for immunodeficiency or corticosteroids for allergic bronchopulmonary aspergillosis is an important initial step.

Airway clearance

Since impaired mucociliary clearance is a defining feature of the disease, enhancing mucus clearance can be sufficient to control disease in a proportion of patients. This can be achieved through simple exercises in many patients (examples include the active cycle of breathing technique and autogenic drainage). Training in these exercises is best conducted by a specialist physiotherapist. Devices such as positive end-expiratory pressure devices can improve the effectiveness of chest clearance techniques. Patients with persistent difficulty with expectoration, despite airway clearance, may benefit from therapies such as isotonic or hypertonic saline through a nebuliser. Oral mucoactive drugs are widely used but have little evidence to support their use. Recombinant DNase which is used in CF was found to be ineffective and potentially harmful in a large bronchiectasis trial and is contraindicated.

Prophylactic antibiotics

These are used to prevent exacerbations in patients with evidence of chronic airway infection. The ERS guidelines suggest considering prophylactic antibiotics in patients with ≥3 exacerbations per year despite appropriate airway clearance and treatment of the underlying cause. Macrolides (azithromycin and erythromycin) reduce exacerbations by 30–50% compared to placebo and may also improve quality of life and symptoms. Risks include induction of antibiotic resistance, gastrointestinal side-effects, hearing loss and induction of resistance in NTM. Adverse effects are dose related and so the lowest effective dose should be used. Excluding NTM prior to prescription is recommended. Prolonged QT interval on the ECG is a concern particularly if macrolides are combined with other drugs that prolong the QT.

Inhaled antibiotics are primarily used to treat patients with chronic infection with *P. aeruginosa* and a meta-analysis suggests they reduce exacerbations by ~30%. Colistin, tobramycin and gentamicin are the most widely used in Europe. The risks include bronchospasm which occurs in 10–30% of cases and induction of antibiotic resistance.

Eradication therapy

This refers to antibiotics given with the intention of preventing chronic infection with pathogenic microorganisms. Eradication therapy should be considered on the first isolation of *P. aeruginosa* or exceptionally on a subsequent isolation of *P. aeruginosa* after sputum samples have been previously negative. Approaches vary but there is evidence that a regimen that includes an inhaled antibiotic may be more effective than oral or intravenous antibiotics alone.

Inhaled corticosteroids and bronchodilators

These are widely used because of the overlap between bronchiectasis and other airway diseases. Use of long-acting bronchodilators in patients with significant breathlessness in bronchiectasis is reasonable and may be effective. Use of inhaled corticosteroids is not recommended unless patients have features of asthma or they are indicated for another reason.

Exercise

Exercise is beneficial for general health and enhances mucus clearance. Pulmonary rehabilitation in bronchiectasis appears to be at least as effective as in COPD and is strongly recommended by the 2017 ERS guidelines.

Surgery

Surgery can be helpful in patients with severe symptoms due to highly localised disease which is amenable to resection. In general, since medical therapy of bronchiectasis can control the disease in most cases, surgery is rarely performed. It should be considered in patients whose disease cannot be controlled with medical therapy or in specific circumstances such as massive haemoptysis or difficult-to-treat NTM infection. Lung transplantation should be considered in appropriate patients.

Management of exacerbations

Exacerbations of bronchiectasis are associated with an increase in symptoms which is greater than normal day to day variation, usually indicating an increased severity and frequency of cough, increase sputum production, a change in sputum characteristics such as colour or viscosity, worsening breathlessness, fatigue, malaise and, sometimes, haemoptysis.

Treatment of an exacerbation should be commenced promptly with 14 days of antibiotics chosen based on the patients previously known microbiology. If patients have never previously had sputum samples sent then antibiotics can be selected based on the most frequent organisms in bronchiectasis patients in that country.

Long-term prognosis and outcomes

The mortality of bronchiectasis patients is greater than the age- and sex-matched general population. Prognosis is, however, highly variable with some patients leading an uncomplicated long-term course and some patients rapidly deteriorating. Patients may require multimodality treatment to achieve control, including management of airway clearance, antibiotic treatment, treatment of comorbidities (including those directly linked to airway inflammation like rhinosinusitis, and those distant from the lungs), and treatment of underlying causes. Some underlying causes of bronchiectasis have worse outcomes such as rheumatoid arthritis and COPD. Patients have a worse prognosis if they have frequent exacerbations or hospital admissions, lower FEV_1, more severe breathlessness measured through the Medical Research Council dyspnoea score, low BMI, older age and more extensive radiological bronchiectasis.

Further reading

- Aksamit TR, *et al.* (2017). Adult patients with bronchiectasis: a first look at the US Bronchiectasis Research Registry. *Chest*; 151: 982–992.
- Chalmers JD, *et al.* (2015). Management of bronchiectasis in adults. *Eur Respir J*; 45: 1446–1462.
- Contarini M, *et al.* (2018). Bronchiectasis: a case-based approach to investigation and management. *Eur Respir Rev*; 27: 180016.
- Flume PA, *et al.* (2018). Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity. *Lancet*; 392: 880–890.
- Haworth CS, *et al.* (2014). Inhaled colistin in patients with bronchiectasis and chronic *Pseudomonas aeruginosa* infection. *Am J Respir Crit Care Med*; 189: 975–982.
- Kapur N, *et al.* (2018). Inhaled corticosteroids for bronchiectasis. *Cochrane database Syst Rev*; 5: CD000996.
- Kelly C, *et al.* (2018). Macrolide antibiotics for bronchiectasis. *Cochrane database Syst Rev*; 3: CD012406.
- Lucas JS, *et al.* (2017). European Respiratory Society guidelines for the diagnosis of primary ciliary dyskinesia. *Eur Respir J*; 49: 1601090.
- Nicolson CH, *et al.* (2012). The long term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. *Respir Med*; 106: 661–667.
- Pasteur MC, *et al.* (2000). An investigation into causative factors in patients with bronchiectasis. *Am J Respir Crit Care Med*; 162: 1277–1284.
- Polverino E, *et al.* (2017). European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J*; 50: 1700629.
- Quint JK, *et al.* (2016). Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. *Eur Respir J*; 47: 186–193.
- Wong C, *et al.* (2012). Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet*; 380: 660–667.

Rare airway diseases

Mouhamad Nasser and Vincent Cottin

Anatomy of the trachea

The trachea is composed of four layers: the inner mucosa, submucosa, cartilage and muscle. The trachea extends from the lower part of the cricoid cartilage in the larynx to the carina, where it divides into the right mainstem bronchus. Around 16–22 C-shaped cartilaginous rings bound by annular ligaments make up the anterolateral tracheal wall. The posterior wall is formed principally of thin bands of smooth muscle. This structure gives its elliptical shape to the trachea that contributes to conformational changes during the respiratory cycle.

The normal coronal diameter of the trachea varies according to sex: 13–25 mm in men and 10–21 mm in women. The sagittal diameter measures 13–27 mm in men and 10–23 mm in women. The normal tracheal wall thickness is between 1 and 3 mm.

The trachea bifurcates into the right and left main bronchi at the level of the second costal cartilage. The right mainstem bronchus is wider, shorter and more vertical than the left mainstem bronchus, which makes it the preferential site for aspiration.

Key points

- Multiplanar reconstruction of HRCT and virtual bronchoscopy assess the airways in their anatomical axis. Minimal intensity projection is helpful to visualise the trachea, bronchi, lung parenchyma and bronchial walls.
- The pattern of flow–volume loops may show an inspiratory plateau in variable extrathoracic disease and an expiratory plateau in variable intrathoracic airway disease.
- Tracheobronchial amyloidosis is characterised by erythematous or yellowish nodules protruding into the tracheobronchial lumen, potentially leading to luminal obstruction.
- Relapsing polychondritis and tracheobronchopathia osteochondroplastica spare the posterior wall of the trachea.
- Monitoring without treatment, bronchoscopic intervention and occasionally, external-beam radiation therapy in tracheobronchial amyloidosis represent the main treatment approaches to rare airway diseases.

Table 1. Classification of rare airway diseases according to anatomical distribution and aetiology

Classification	Focal	Diffuse	Diffuse with sparing of the tracheal posterior wall
Primary	Idiopathic subglottic stenosis	Mounier-Kuhn syndrome	Relapsing polychondritis Tracheobronchopathia osteochondroplastica
Secondary	Post-intubation stenosis Tracheal papillomatosis Post-infection stenosis	Secondary tracheobronchomegaly Granulomatosis with polyangiitis Tracheobronchial amyloidosis Sarcoidosis Inflammatory bowel disease	

Clinical manifestations

Dyspnoea generally occurs on exercise when narrowing of the airways represents ≥80% of the luminal diameter and occurs at rest when narrowing exceeds 90%. Cough and stridor may also be present. Intrathoracic narrowing produces expiratory stridor while extrathoracic involvement is responsible for inspiratory stridor and dyspnoea.

Classification

Airway diseases can be classified according to anatomical distribution (including involvement or sparing of the tracheal posterior wall) and aetiology (table 1).

Diagnosis

Chest radiography has a limited role in the evaluation of airway diseases, even proximally. However, tracheal stricture or tracheobronchomegaly may be seen.

Optimal imaging evaluation of airway diseases is obtained by CT of the chest using nonaxial multiplanar reconstruction to evaluate the airways in their anatomical axis, and minimal intensity projection (MiniP) for better visualisation of low-attenuation organs (trachea, bronchi and lung parenchyma) and of the bronchial wall. CT virtual bronchoscopy may occasionally replace flexible bronchoscopy with better tolerance and often higher sensitivity.

Flexible bronchoscopy, however, is the modality of choice to characterise and biopsy tracheobronchial lesions. Endobronchial ultrasonography may be used to distinguish cartilage and submucosal involvement. Positron emission tomography scanning may also contribute.

Pulmonary function tests, and especially the pattern of flow–volume loop, are key to assessing functional impairment; however, they may underestimate the severity of dynamic stenosis. An inspiratory plateau may be seen in variable extrathoracic disease as the intraluminal pressure decreases during inspiration. An expiratory plateau may be seen in variable intrathoracic narrowing.

Primary tracheobronchial amyloidosis

Amyloidosis, localised or systemic, is a protein deposition disease characterised by the accumulation of insoluble amyloid fibrils within the extracellular space, with a core structure of antiparallel β-strands. Pulmonologists may encounter amyloidosis as the pulmonary parenchymal involvement of systemic amyloidosis, as systemic amyloidosis complicating a chronic lung condition, or as localised pulmonary and respiratory tract involvement.

Tracheobronchial amyloidosis exclusively seen as a localised amyloid deposition represents 0.5% of all symptomatic tracheobronchial lesions requiring treatment. It is characterised by erythematous or yellowish nodules protruding into the tracheobronchial lumen, potentially leading to luminal obstruction. Diffuse submucosal infiltration may present as the only manifestation. As in all forms of amyloidosis, tracheobronchial nodules have a tendency to bleed because amyloid proteins deposit preferentially along the vessels and may impair vasoconstriction. Calcifications when present can involve the posterior tracheal wall.

Clinical manifestations depend on the type of involvement. Stridor, dyspnoea and cough are characteristics of nodular airway disease. Recurrent post-obstructive pneumonias, peribronchial thickening or atelectasis are seen when distal bronchial lesions are present. Narrowing of airways can cause an obstructive airflow defect.

In addition to CT, MRI may demonstrate more specific features. Biopsy confirmation is required for the diagnosis. Positive Congo Red staining and apple-green birefringence under polarised light are characteristic findings. Once amyloidosis is confirmed, amyloid deposits should be examined by immunohistochemistry or mass spectrometry-based proteomic analysis to determine the nature of the protein. The vast majority of localised amyloid deposits are of the AL (amyloid light-chain) type, often associated with subtle focal monoclonal B-cell proliferation confined to the affected anatomical site.

Although localised, tracheobronchial amyloidosis may cause infectious pneumonia or respiratory failure and one in three patients will die from the disease over a decade. Close monitoring of the disease by imaging and physiology is mandatory.

Treatment needs to be tailored to each patient. 'Watch and wait' is often the best option. Luminal stenosis may be treated with a Nd:YAG (neodymium-doped yttrium aluminium garnet) laser, which allows coagulation control in cases of bleeding. External-beam radiation therapy, which suppresses the local plasma cell clone, has been used, especially in bulky or distal disease not amenable to bronchoscopic intervention. Diffuse involvement of smaller airways often indicating a more systemic disease process generally requires a chemotherapeutic approach.

Tracheobronchopathia osteochondroplastica

This exceedingly rare idiopathic disease is characterised by the nonmalignant growth of bone and/or cartilaginous submucosal nodules extending into the tracheobronchial lumen. Airway obstruction may occur in severe forms.

Only a minority of patients are smokers or ex-smokers. An inspiratory or expiratory plateau may be present in 10–20% of cases. Tracheobronchial amyloidosis and atrophic rhinitis (with progressive nasal mucosal atrophy and bone resorption) are commonly associated.

The diagnosis is based on the typical appearance of submucosal nodules on bronchoscopy. As the nodules arise from the tracheobronchial cartilage, the posterior tracheal wall is usually spared. A biopsy is rarely needed. The main differential diagnoses are amyloidosis and papillomatosis, which can involve the tracheal posterior wall.

The natural course of the disease is either stable or very slowly progressive. Treatment is supportive. Interventional endoscopy is rarely required.

Mounier-Kuhn syndrome and tracheobronchomegaly

Tracheobronchomegaly consists of marked dilatation of the trachea and major bronchi. Congenital tracheobronchomegaly (Mounier-Kuhn syndrome) is due to muscular mucosal thinning, atrophy of longitudinal muscles and elastic fibres, and absence of the myenteric plexus in the trachea and major bronchi (analogous to Hirschprung disease or achalasia of gastric cardia). Unlike Williams–Campbell syndrome, the calibre of the fourth- to sixth-order bronchi is normal.

Tracheobronchomegaly can be idiopathic (Mounier-Kuhn syndrome) or secondary to cutis laxa, Ehlers–Danlos, Marfan syndrome, ankylosing spondylitis or fibrotic lung diseases (idiopathic pulmonary fibrosis and pleuroparenchymal fibroelastosis).

The prevalence is between 0.4% and 1.6% of patients with respiratory symptoms. Men are more commonly affected than women, with sex ratio of 8/1, and diagnosis may be made at any age.

Bronchomegaly is defined by a coronal diameter of the right and left main bronchus exceeding 2.4 and 2.3 cm, respectively. Tracheobronchomegaly is easily suspected on chest CT or sometimes on chest radiography when the transverse coronal diameter of the trachea (measured 2 cm above the carina) exceeds 3 cm. Tracheal diverticulosis and tracheobronchial dyskinesia may be associated in about one third of cases, and bronchiectasis in nearly half of cases.

Tracheobronchomegaly is usually asymptomatic. However, some patients present with cough, dyspnoea and recurrent lower respiratory infections due to bronchiectasis. It is usually a nonprogressive disease with no specific treatment indicated. Influenza and pneumococcal vaccination should be considered in patients with recurrent lower respiratory tract infections.

Idiopathic subglottic stenosis

Idiopathic subglottic stenosis is characterised by the circumferential narrowing of the subglottic larynx and upper trachea. It is almost exclusively found in women. Gastro-oesophageal reflux disease present in more than half of cases may be partly causal.

Patients often experience exertional dyspnoea and may be misdiagnosed with asthma. The diagnosis is made by fibreoptic bronchoscopy. EBUS (endobronchial ultrasound) may differentiate it from relapsing polychondritis, showing thickening of the lamina propria with intact cartilage. Management is empirical, and can include proton pump inhibitors, dilatation by interventional endoscopy, surgical laryngotracheal resection and reconstruction, or local application of mitomycin C or intralesional corticosteroid injections.

Relapsing polychondritis

This extremely rare autoimmune disease (prevalence of 4.5–9 cases per million persons) predominantly affects the cartilaginous tissue. Chondritis of the ear pinna is the most common (90%) and expressive manifestation of the disease. Involvement of the trachea and the main bronchi is common and represents, along with cardiac involvement, an important cause of mortality. The disease evolves with bouts of flare-up, endangering the patient's life, with cough, dysphonia, hoarseness, aphonia and stridor.

On examination, the anterior thyroid cartilage and the trachea are usually tender and responsible for neck pain. Tracheal cartilage calcifications may be seen and should be differentiated from age-related calcifications, tracheobronchopathia osteochondroplastica and tracheobronchial amyloidosis. Posterior wall sparing is helpful to distinguish it from amyloidosis. Histopathology is not characteristic and biopsy should be avoided in the acute phase of the disease as it may precipitate airway collapse. Patients often are asymptomatic between exacerbations, with normal endoscopic appearance or narrowing of the tracheobronchial lumen. No autoantibody is found.

The disease course is unpredictable, with repetitive attacks damaging the airways. Saddle nose deformity may develop over time as in granulomatosis with polyangiitis or sarcoidosis. Corticosteroids and immunosuppressive drugs are the mainstay of treatment. Tracheostomy may eventually be required.

Granulomatosis with polyangiitis

Tracheobronchial involvement is present in 15–55% of cases of granulomatosis with polyangiitis and consists mostly of subglottic inflammation, which may progress to subglottic stenosis. There is generally no necrotising granulomas or vasculitis in biopsied tissue.

Subglottic stenosis may be the only manifestation of disease and may progress independently from the systemic disease. It may relapse after systemic and endoscopic treatment, requiring local injections of steroids, or occasionally surgery once inflammation has regressed.

Other tracheobronchial manifestations include concentric lower tracheal or bronchial inflammation or stenosis, synechial bands resulting in obliteration of smaller airways, submucosal tunnels, polypoid mass lesions (inflammatory pseudotumours) and less commonly, tracheobronchomalacia.

Sarcoidosis

Involvement of large airways in uncommon in sarcoidosis, and it more frequently affects lobar and segmental airways than the trachea and main bronchi. Blind endobronchial biopsy in asymptomatic patients may show granulomatous inflammation in ~60% of cases. Isolated involvement of large airways is rare.

The airway manifestations of sarcoidosis are extremely variable, including benign mucosal inflammation and erythema, granular mucosa, yellowish mucosal plaques, mucosal nodules, bronchial stenosis, airway distortion, airway compression, and hypersensitivity. An endoscopic cobblestone appearance may lead to significant airway obstruction. Systemic corticosteroids are the mainstay of treatment. Inhaled steroids may be beneficial on cough.

Miscellaneous causes

Rheumatoid arthritis may cause bronchiectasis predominating in the lower lobes, which can precede the joint involvement by decades. Centrilobular nodules and branching opacities suggestive of bronchiolar involvement are often associated. Sjögren syndrome and, rarely, systemic sclerosis may also lead to symptomatic airway diseases that are usually nonobstructive. Other rare conditions that may cause airway impairment are tracheobronchial papillomatosis, inflammatory bowel disease and ankylosing spondylarthritis.

Further reading

- Girard C, *et al.* (2015). Tracheobronchial stenoses in granulomatosis with polyangiitis (Wegener's): a report on 26 cases. *Medicine*; 94: e1088.
- Leske V, *et al.* (2001). Tracheobronchopathia osteochondroplastica: a study of 41 patients. *Medicine*; 80: 378–390.
- Maldonado F, *et al.* (2015). Orphan tracheopathies. *In*: Cottin V, *et al.*, eds. Orphan Lung Diseases, a Clinical Guide to Rare Lung Disease. London, Springer; pp. 91–111.
- Mathian A, *et al.* (2016). Relapsing polychondritis: a 2016 update on clinical features, diagnostic tools, treatment and biological drug use. *Best Pract Res Clin Rheumatol*; 30: 316–333.
- Morgenthau AS, *et al.* (2011). Sarcoidosis of the upper and lower airways. *Expert Rev Respir Med*; 5: 823–833.
- Venner CP, *et al.* (2015). Amyloidosis and the respiratory tract. *In*: Cottin V, *et al.*, eds. Orphan Lung Diseases, a Clinical Guide to Rare Lung Disease. London, Springer; pp. 91–111.

Congenital airway disease

Ernst Eber

This section gives a short overview of congenital airway disease (CAD) (table 1). The majority of children with CAD are already symptomatic in the neonatal period or in infancy; only rarely is CAD discovered incidentally. Airway endoscopy is the most important diagnostic procedure. Other essential diagnostic techniques are MRI and CT, frequently including angiography.

In children with CAD, respiratory and gastrointestinal morbidity may be significant. Thus, they should be regularly evaluated by a multidisciplinary team. The transition of young adults from paediatric care to an adult physician with expertise in CAD is recommended. Depending on the type and severity of CAD, conservative or surgical management options may be chosen. With airway growth, mild-to-moderate airway stenoses frequently become less prominent in the first years of life. Thus, conservative symptomatic treatment and support is often the preferred approach. In most patients the long-term prognosis is favourable.

Nasopharyngeal airway

Choanal stenosis and atresia

This is one of the most common upper airway malformations (~1 in 8000 births). About two-thirds of patients show associated congenital anomalies, *e.g.* CHARGE association, characterised by coloboma of the eye, heart defects, atresia of the nasal choanae, retardation of growth and/or development, genital and/or urinary abnormalities, and ear abnormalities and deafness.

Bilateral choanal atresia causes immediate respiratory distress at birth; the more common unilateral lesions are often not detected until later in childhood (*e.g.* if the patent nostril is occluded during respiratory infections).

Key points

- Airway anomalies may be part of complex syndromes and, in many cases, are associated with other congenital anomalies.
- With airway growth, mild-to-moderate stenoses in the first years of life frequently become less prominent.
- Depending on the type and extent of the malformation, conservative or surgical management options are chosen on an individual basis.
- With adequate management, in most patients the long-term prognosis is favourable.

Table 1. Important congenital airway diseases

Nasopharyngeal airway
Choanal stenosis and atresia
(Pierre) Robin sequence
Craniofacial malformations
Larynx
Laryngeal atresia
Laryngeal web
Subglottic stenosis
Laryngomalacia (infantile larynx)
Laryngeal cyst
Laryngeal (laryngo-tracheo-oesophageal) cleft
Trachea and bronchial tree
Tracheal agenesis and atresia
Tracheo-oesophageal fistula and oesophageal atresia
Isolated tracheo-oesophageal fistula (H-type fistula)
Tracheomalacia
Tracheal stenosis
Tracheal bronchus and other topographic anomalies
Bronchial atresia
Bronchomalacia
Bronchial stenosis

A nasal airway should be established as soon as possible, usually by a transnasal approach. In severe cases, transpalatal surgery may be required.

(Pierre) Robin sequence

This anomaly is characterised by micrognathia, glossoptosis and (pharyngeal) airway obstruction of variable severity. More than half of the patients have an associated syndrome, and frequently also a cleft palate or other airway pathologies. As the mandible grows forward with age, airway and feeding problems may gradually resolve during the first year of life.

There is a wide range of treatment options, from prone positional therapy to surgical procedures. Patients with Robin sequence should be cared for by a multidisciplinary team.

Other craniofacial anomalies

Many syndromic craniofacial anomalies (typically characterised by mandibular or maxillary hypoplasia) can affect upper airway patency. A narrowed nasopharynx with associated adenotonsillar hypertrophy, midface hypoplasia and hypertrophy of the tongue can cause airway compromise in patients with Down syndrome.

Larynx

Laryngeal atresia

This is a life-threatening malformation and, in the past, virtually all affected newborns died. Antenatal ultrasound scans may allow diagnosis of congenital high airway obstruction syndrome related to laryngeal (or upper trachea) atresia and help facilitate management, including *ex utero* intrapartum treatment (EXIT). Without antenatal diagnosis newborns with laryngeal atresia may only survive with emergency tracheostomy immediately after

Table 2. Grading system for subglottic stenoses

Grade I	Up to 50% obstruction of the lumen
Grade II	51–70% obstruction of the lumen
Grade III	>70% obstruction of the lumen (any detectable lumen)
Grade IV	No detectable lumen

Data from Myer *et al*. (1994).

birth. The prognosis also depends on the presence of associated anomalies, *e.g.* VACTERL association, characterised by vertebral defects, anal atresia, cardiac defects, tracheo-oesophageal fistula (TOF), renal anomalies and limb abnormalities.

Laryngeal web

This anomaly is usually located at the level of the glottis, may be complete or incomplete, and can vary in thickness. Incomplete laryngeal webs are strongly associated with the velocardiofacial syndrome. Treatment options include (laser) excision and dilation. The prognosis mainly depends on the extent of the lesion.

Subglottic stenosis

Congenital subglottic stenosis is the second most common laryngeal malformation. Membranous subglottic stenosis is more common than the cartilaginous form. Myer *et al*. (1994) proposed a grading system for subglottic stenoses based on endotracheal tube sizes (table 2).

The clinical presentation depends on the grade of the stenosis and ranges from severe respiratory distress at birth to the development of stridor within the first months of life (recurrent or atypical croup). Children with congenital subglottic stenosis are at risk of developing additional acquired subglottic stenosis due to airway trauma (*e.g.* endotracheal intubation).

Congenital subglottic stenosis generally improves with airway growth; a conservative approach is recommended whenever possible, and surgery should be reserved for severe forms.

Laryngomalacia (infantile larynx)

This is the most common congenital laryngeal anomaly (50–75%) and the most common cause of persistent stridor in children (~60%). According to Holinger *et al.* (1997), five types of laryngomalacia can be distinguished (table 3); two or more may occur simultaneously. Laryngomalacia is frequently associated with other airway lesions and with gastro-oesophageal reflux (GOR).

Table 3. Types of laryngomalacia

Type 1	Inward collapse of the aryepiglottic folds, primarily the cuneiform cartilages which are often enlarged
Type 2	Long, tubular epiglottis (pathologic exaggeration of the normal omega shape)
Type 3	Anterior, medial collapse of the arytaenoid cartilages
Type 4	Posterior displacement of the epiglottis against the pharyngeal wall or inferior collapse to the vocal cords
Type 5	Short aryepiglottic folds

The natural history is characterised by onset of inspiratory stridor usually within the first 4–6 weeks of life. Stridor varies with posture and airflow, is loudest with increased ventilation (*e.g.* crying, agitation and feeding) and worsens during respiratory tract infections. In (very rare) severe cases with significant airway obstruction, complications such as failure to thrive, obstructive apnoeas, pulmonary hypertension and cor pulmonale may develop.

In the majority of cases, no specific therapeutic measures are needed. For severe cases, surgical treatment options (*e.g.* supraglottoplasty) exist. In isolated forms prognosis is excellent.

Laryngeal cyst

Congenital laryngeal cysts are commonly located at the aryepiglottic folds or at the epiglottis. A laryngocele is a rare form of a laryngeal cyst, which originates from the laryngeal ventricle, consists of an air-filled saccule and may be difficult to diagnose. The treatment of choice is resection of the cyst.

Laryngeal (laryngo-tracheo-oesophageal) cleft

Posterior laryngeal clefts are rare, may be familial and associated with other anomalies of the trachea or the oesophagus (*e.g.* TOF) and with multiple congenital anomalies of other organ systems. Several types of posterior clefts are distinguished (table 4); the most common (~50%) is type 1 cleft which should be suspected in children with laryngomalacia. Anterior laryngeal clefts (*e.g.* bifid epiglottis) are very rare.

Children with type 1 clefts may be asymptomatic; thus, diagnosis is often delayed in patients with minor clefts. A cleft may be difficult to diagnose with flexible bronchoscopy, as manipulation of the posterior commissure may be necessary to detect the cleft; rigid bronchoscopy is often the preferred technique for the documentation of the pathology.

In the absence of complicating factors treatment is not required for many type 1 clefts. Minor clefts (types 1 and 2) may be corrected endoscopically. Surgical repair often has to be performed with cardiopulmonary bypass or extracorporeal membrane oxygenation. Prognosis depends on the type of the cleft, gestational age and associated anomalies. It is favourable for patients with type 1–3 clefts.

Trachea and bronchial tree

Tracheal agenesis and atresia

These are rare anomalies ranging from complete tracheal agenesis to short-segmental atresia, commonly associated with broncho-oesophageal fistula, TOF or other anomalies in various organ systems (*e.g.* VACTERL association). Similar to laryngeal

Table 4. Classification system for laryngeal clefts

Type 1	Supraglottic interarytenoid cleft extending inferiorly no further than the vocal cord level
Type 2	Cleft with extension below the vocal cord level (cricoid cartilage partially involved)
Type 3	Cleft extending through the cricoid cartilage with or without extension into the cervical trachea
Type 4	Cleft with extension into the thoracic trachea (may extend as far as the carina)

Data from Benjamin *et al*. (1989).

atresia these anomalies are usually lethal; after antenatal diagnosis an EXIT procedure may be life-saving. Survival also depends on the presence of associated anomalies.

TOF and oesophageal atresia

Oesophageal atresia is relatively common (~1 in 3500 births). About 30% of affected children are born prematurely, and more than 50% have associated anomalies (*e.g.* VACTERL association). The most common type of oesophageal atresia (~85%) is characterised by an upper blind pouch and a fistula between the lower trachea and the lower oesophagus. Structural anomalies of the tracheal wall such as abnormally shaped or hypoplastic tracheal cartilages or a widened pars membranacea (*i.e.* tracheomalacia) are common.

Depending on the type of oesophageal atresia, associated anomalies and the clinical status of the patient various surgical techniques are recommended. Post-operative complications include oesophageal stenosis and recurrence of the TOF. GOR and dysphagia are very common and contribute to respiratory morbidity. Recurrent aspiration is frequent and causes bronchitis and pneumonia. Tracheomalacia may be severe, sometimes even life-threatening ('blue spells' and 'dying spells'). Many children show the typical brassy 'TOF cough', which is still present in up to 40% of adults. A missed diagnosis of laryngeal (laryngo-tracheo-oesophageal) cleft, a second fistula or a recurrent fistula should be considered in patients with pronounced respiratory symptoms.

Survival mainly depends on birth weight, associated malformations and pulmonary complications. Mortality in children with a birth weight >2500 g and without other anomalies is close to zero. In surviving children the long-term outcome is good.

Isolated TOF (H-type fistula)

This malformation is much rarer than a TOF in association with oesophageal atresia, and commonly is not associated with other anomalies. Usually, the fistula is located in the extrathoracic part of the trachea and has a narrow lumen.

Rigid airway endoscopy is superior to flexible endoscopy in establishing the diagnosis. Treatment is surgical and consists of ligation and division of the fistula. Long-term prognosis is excellent, unless diagnosis is delayed until late childhood or even adulthood. The latter may result in considerable respiratory morbidity due to recurrent aspiration and infection.

Tracheomalacia

This common anomaly (~1 in 2000) is characterised by weakness of the tracheal wall, due to reduction and/or atrophy of the longitudinal elastic fibres of the pars membranacea, a widened pars membranacea, or impaired cartilage integrity ('immaturity'). It can be primary or secondary, and may be localised or generalised. Primary tracheomalacia may be found in association with oesophageal atresia, Down syndrome, Ehlers–Danlos syndrome, and with laryngomalacia or bronchomalacia. Localised secondary tracheomalacia may occur as a consequence of compression (*e.g.* double aortic arch). Feeding may cause 'dying spells' as food in the oesophagus may compress the malacic trachea.

Intrathoracic tracheomalacia leads to dynamic airway compression on expiration, in particular during increased respiratory effort and coughing, or during respiratory infections. Tracheal collapse may result in retention of secretions from the lower airways, which in turn may cause bronchopulmonary infections. Tracheomalacia is frequently misdiagnosed as bronchial asthma or other respiratory conditions.

Flow–volume curves make it possible to distinguish between extra- and intrathoracic obstruction and between variable (tracheomalacia) and fixed (tracheal stenosis) obstruction. Flexible airway endoscopy during spontaneous breathing is the diagnostic procedure of choice. CT and MRI (with angiography) are complementary techniques, in particular when extrinsic compression is suspected.

Generally, in patients with isolated tracheomalacia airway function improves with age, as the airway grows and the airway wall stiffens. Thus, most patients can be managed conservatively, with chest physiotherapy and antibiotics for secondary infections. Other treatment options include aortopexy in localised tracheomalacia and long-term application of positive airway pressure *via* tracheal cannula in generalised forms. Stents may be effective in diffuse tracheomalacia but severe complications have been reported. Thus, stents should only be employed as a last resort when all other conservative and surgical options have failed to wean patients off the ventilator over a long period of time or have failed to relieve life-threatening obstructive episodes. Treatment and prognosis depend on the type and severity of the malacia and on associated anomalies.

Tracheal stenosis

This anomaly is less common than tracheomalacia. Membraneous stenoses (webs) are less common than anomalies of the tracheal cartilages. Complete cartilaginous rings (‘napkin ring cartilages’) mainly occur in the intrathoracic trachea; sometimes the whole trachea is affected. The shape of the stenosis can be hourglass or funnel-like (carrot-shape, ‘rat-tail’ trachea). Tracheal stenoses are frequently associated with other anomalies such as left pulmonary artery sling, abnormal bronchial arborisation (*e.g.* tracheal bronchus) or a single lung. Various classifications have been proposed, based on the length of stenosis, the severity of symptoms, and according to bronchial involvement.

Congenital tracheal stenosis may be life-threatening or may only be detected incidentally. Unless severe stenosis precludes a complete endoscopic examination, flexible bronchoscopy is helpful in defining airway anatomy including bronchial arborisation and in detecting possibly associated tracheo- and/or bronchomalacia. Usually, CT or MRI are necessary to define the extent of the lesion and to confirm or rule out compression by an extrinsic lesion.

As tracheal stenosis may improve with airway growth, conservative and symptomatic treatment (including chest physiotherapy and antibiotics) are recommended whenever possible. Surgical options for severe stenoses include tracheostomy to bypass a stenosis, resection and primary anastomosis for short segment stenosis, and slide tracheoplasty for long segment stenosis in specialised referral centres. Treatment and prognosis depend on the type and severity of the stenosis and on associated anomalies.

Tracheal bronchus and other topographic anomalies

Topographic anomalies are the most common anomalies of the tracheobronchial tree. A tracheal bronchus (‘pig bronchus’) may be associated with other anomalies in the tracheobronchial tree or in other organ systems. It originates from the right tracheal wall and supplies either an accessory segment, the apical segment of the right upper lobe, or the whole right upper lobe.

These anomalies are usually asymptomatic and thus only incidentally detected. If structural anomalies (*e.g.* malacia) are present, the anomaly may result in recurrent or persistent pneumonia or atelectasis, and later bronchiectasis in the respective segment or lobe. In symptomatic patients, chest physiotherapy and antibiotics are the treatment of choice. When problems persist despite conservative measures, resection of the affected segment or lobe may be necessary.

Topographic anomalies of the whole lung (*e.g.* situs inversus and bronchial isomerism) are usually associated with topographic anomalies of the heart and/or abdominal organs (*e.g.* Ivemark syndrome with asplenia).

Bronchial atresia

This rare anomaly is frequently associated with congenital lung malformations. A lobar or (sub)segmental bronchus ends blindly, separated by a short gap from the distally located bronchial tree supplying the lobe or (sub)segment. The clinical picture varies widely from the neonate with respiratory distress to the asymptomatic adult. Resection of the lesion is usually recommended.

Bronchomalacia

Bronchomalacia is characterised by abnormal weakness of the bronchial wall. Localised forms are distinguished from generalised forms (*e.g.* Williams–Campbell syndrome), and primary from secondary forms; the latter are usually caused by vascular compression. Bronchomalacia is frequently associated with tracheomalacia, and the left main bronchus is predominantly affected.

Signs and symptoms depend on severity; some children only develop symptoms during respiratory infections. Gradual improvement may be expected with age and airway growth. Only a minority of patients with significant respiratory problems requires treatment apart from conservative measures (chest physiotherapy and antibiotics). Prognosis mainly depends on associated anomalies.

Bronchial stenosis

This anomaly is rare and predominantly occurs in mainstem (left > right) and lobar bronchi. Retention of secretions may lead to bronchopulmonary infections and the development of bronchiectasis. As patients tend to show improvement with age and airway growth, conservative management is recommended. Resection and primary anastomosis may be necessary for severe short segment stenosis.

Further reading

- Abel RM, *et al.* (2012). Congenital lung disease. *In*: Wilmott RW, *et al.*, eds. Kendig and Chernick's disorders of the respiratory tract in children. 8th Ed. Philadelphia, Elsevier, pp. 317–357.
- Benjamin B, *et al.* (1989). Minor congenital laryngeal clefts: diagnosis and classification. *Ann Otol Rhinol Laryngol*; 98: 417–420.
- Boogaard R, *et al.* (2005). Tracheomalacia and bronchomalacia in children: incidence and patient characteristics. *Chest*; 128: 3391–3397.
- Eber E (2006). Adult outcome of congenital lower respiratory tract malformations. *Swiss Med Wkly*; 136: 233–240.
- Eber E (2010). Congenital and acquired abnormalities of the upper airways. *In*: Priftis KN, *et al.*, eds. Paediatric bronchoscopy. Progress in respiratory research. Vol. 38. Basel, Karger, pp. 120–129.
- Eber E, *et al.* (2017). ERS statement: interventional bronchoscopy in children. *Eur Respir J*; 50: 1700901.

- Evans KN, *et al.* (2011). Robin sequence: from diagnosis to development of an effective management plan. *Pediatrics*; 127: 936–948.
- Holinger LD, *et al.*, eds (1997). Pediatric laryngology and bronchoesophagology. Philadelphia, Lippincott-Raven.
- Laberge JM, *et al.* (2008). Congenital malformations of the lungs and airways. *In*: Taussig LM, *et al.*, eds. Pediatric respiratory medicine. 2nd Edn. St. Louis, Mosby, pp. 907–941.
- Myer CM 3rd, *et al.* (1994). Proposed grading system for subglottic stenosis based on endotracheal tube sizes. *Ann Otol Rhinol Laryngol*; 103: 319–323.
- Pfleger A, *et al.* (2016). Assessment and causes of stridor. *Paediatr Respir Rev*; 18: 64–72.
- Pohunek P, *et al.* (2010). Congenital and acquired abnormalities of the lower airways. *In:* Priftis KN, *et al.*, eds. Paediatric bronchoscopy. progress in respiratory research. Vol. 38. Basel, Karger, pp. 130–140.
- Speggiorin S, *et al.* (2012). A new morphologic classification of congenital tracheobronchial stenosis. *Ann Thorac Surg*; 93: 958–961.

Upper respiratory tract infections

Gernot Rohde

Prevalence

URTIs usually occur during the cold months, mainly due to overcrowding inside buildings. The mean frequency is two to four episodes annually for adults. In children, it is higher. Antigenic variation of hundreds of respiratory viruses allows repeated circulation in the community.

Spectrum

The upper respiratory tract comprises the airways above the vocal cords and consists of the nose, paranasal sinuses, pharynx and larynx. The most prevalent illness is the common cold (rhinosinusitis), followed by sinusitis, pharyngitis/tonsillitis, laryngitis, and sometimes tracheobronchitis (table 1).

The onset of symptoms usually begins after 1–3 days after exposure to a microbial pathogen. The duration of the symptoms is typically 7–10 days but may persist longer.

Transmission and predisposition

Transmission of pathogens is by aerosol, droplet or direct hand-to-hand contact. The pathogens invade the respiratory epithelium of the corresponding area.

Key points

- Upper respiratory tract infections (URTIs) are the most common infectious illness in the general population, and are the leading cause of missed work and school.
- Most URTIs are viral in origin, and typical agents are rhinoviruses, coronaviruses, adenoviruses, coxsackieviruses, influenza and parainfluenza viruses, human metapneumovirus, and respiratory syncytial virus.
- URTIs rarely cause permanent sequelae or death, but can progress to otitis media, bronchitis, bronchiolitis, pneumonia, sepsis, meningitis, intracranial abscess and other infections.
- Diagnosis is usually purely clinical; diagnostic investigations should only be performed in special circumstances, such as influenza, group A streptococcal pharyngitis, infectious mononucleosis and pneumonia.
- Infection will often be self-limiting, with no specific treatment necessary; the only indications for antibiotic treatment are group A streptococcal pharyngitis, bacterial sinusitis and pertussis.

Table 1. Signs and symptoms

URTI	Symptoms	Signs
Common cold	Nasal congestion mucopurulent nasal discharge, sneezing, sore throat, halitosis	Low-grade fever, nasal vocal tone, inflamed nasal mucosa
Sinusitis	Unilateral facial pain, maxillary toothache, headache, purulent nasal discharge	Swelling, redness, tenderness to palpation or percussion overlying the affected sinuses, abnormal transillumination
Pharyngitis	Sore throat, odynophagia or dysphagia, fever, absence of cough, halitosis	Pharyngeal erythema and exudate, palatal petechiae (doughnut lesions), tender anterior cervical lymphadenopathy, scarlatiniform rash, pharyngeal or palatal vesicles and ulcers (herpangina), tonsillar hypertrophy
Laryngitis	Hoarseness, voicelessness, dry cough, odynophagia or dysphagia, halitosis	Low-grade fever, cervical lymphadenopathy, inspiratory stridor, tachypnoea

Sinusitis and acute bronchitis are often preceded by a common cold. There are predisposing conditions such as allergic rhinoconjunctivitis, nasal septum deviation, immunodeficiency or cocaine abuse. Smoking or exposure to second-hand smoke and travel are additional risk factors.

Pathogens

Most URTIs are viral in origin. More than 200 different viruses are known to cause the common cold. Typical viral agents that cause URTIs are rhinoviruses, coronaviruses, adenoviruses, coxsackieviruses, influenza and parainfluenza viruses, human metapneumovirus, respiratory syncytial virus (RSV) and others.

Group A, but also group C and G, streptococci can cause pharyngitis (10–20% of cases), as well as other bacteria like *Neisseria gonorrhoeae*, *Corynebacterium diphtheriae* and atypical bacteria (*Chlamydia* and *Mycoplasma*). *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* can be the bacterial cause of rhinosinusitis or tracheobronchitis. *Bordetella pertussis* or *Bordetella parapertussis* are the cause of whooping cough associated with laryngotracheitis.

Complications

URTIs usually are self-limiting and rarely cause permanent sequelae or death. However, they can progress to otitis media, bronchitis, bronchiolitis, pneumonia, sepsis, meningitis, intracranial abscess and other infections. Specific complications can occur with untreated group A streptococcal pharyngitis resulting in acute rheumatic fever (ARF), acute glomerulonephritis, peritonsillar abscess and toxic shock syndrome. Sinusitis can extend into surrounding deep tissue leading to orbital cellulitis, subperiosteal abscess, orbital abscess, frontal and maxillary osteomyelitis, subdural abscess, meningitis and brain abscess. Epiglottitis, a presentation of laryngitis caused by *H. influenzae* type B (Hib), poses a risk of death due to sudden airway obstruction and other complications, including septic arthritis, meningitis, empyema and mediastinitis.

Diagnosis

In most cases, the diagnosis is purely clinical. History, inspection, palpation, percussion and auscultation (table 1) are sufficient. Additional diagnostic investigations should only be performed in special circumstances. These include suspicion of:

- influenza (perform pharyngeal swab for PCR)
- group A streptococcal pharyngitis (perform pharyngeal swab for rapid antigen detection test)
- infectious mononucleosis (there are usually additional symptoms such as hepatosplenomegaly and lymphocytosis; perform mononucleosis spot test in blood)
- pertussis (perform serology or PCR on respiratory specimens, mostly nasopharyngeal swab)

Differential diagnosis

Influenza

Influenza viruses can cause mild URTIs but also systemic disease. The definition of influenza-like illness is fever (>38.5ºC) and one of the following: cough, sore throat, headache and muscle ache.

Allergic rhinoconjunctivitis

Allergic rhinoconjunctivitis is characterised by oedema of the conjunctiva, itching and increased lacrimation in addition to symptoms of rhinitis. Consider seasonal variations related to allergen exposure.

Acute thyroiditis

Acute thyroiditis can present as a sore throat, a common symptom in URTIs. Investigation of thyroid hormones, thyroid-specific autoantibodies, ultrasound and radioactive iodine uptake can support diagnosis.

Gastro-oesophageal reflux

Gastro-oesophageal reflux disease can clinically present as laryngopharyngitis and/or tracheobronchitis. History and in more severe cases oesophagogastroduodenoscopy should be performed.

Granulomatosis with polyangiitis

Granulomatosis with polyangiitis should be considered in patients with sinusitis not responding to therapy. Classic antineutrophil cytoplasmic antibodies and biopsy are key to diagnosis.

Asthma

Asthma should be considered in patients with a nonresolving cough for >3 weeks.

Treatment

The vast majority of URTIs are viral in origin. In most cases the infection will be self-limiting and no specific treatment is necessary. Sufficient fluid intake should be advocated. The effect of zinc and vitamin C is still debated. Echinacea seems to be effective in prevention and treatment of the common cold. Nonsteroidal anti-inflammatory drugs relieve fever, headache and malaise. In general, there is no role for antibiotic therapy in the management of common cold or any mild URTI. The only indications for antibiotic treatment are:

- group A streptococcal pharyngitis (oral penicillin or macrolide for 10 days)
- bacterial sinusitis, usually a sinusitis not resolving within 7 days (aminopenicillin with or without a β-lactamase inhibitor, second or third generation cephalosporins, macrolides or trimethoprim-sulfamethoxazole for 7–10 days)
- pertussis (macrolides, alternatively erythromycin or trimethoprim-sulfamethoxazole or doxycyclin for 7 days)

Nasal decongestants decrease symptoms in rhinitis and sinusitis, and topical nasal steroids improve sinusitis. Confirmed cases of influenza can be considered for therapy with neuraminidase inhibitors according to Centers for Disease Control and Prevention guidelines. New treatment options for the most prevalent respiratory pathogens, human rhinoviruses and RSV, are still under development.

Prevention

Direct hand-to-hand contact is an important mechanism of pathogen transmission. Hence, frequent hand washing or disinfection in healthcare settings can limit the spread of infection significantly. Influenza vaccination has been shown to be very beneficial and has to be advocated. In children, the routine administration of the Hib vaccine has practically eradicated Hib as a cause of URTI. A herd effect could be demonstrated, as the introduction of the pneumococcal vaccine in children correlated with a significant reduction in invasive pneumococcal disease in adults.

Further reading

- Centers for Disease Control and Prevention. Influenza (flu). www.cdc.gov/flu Date last updated: April 26, 2019.
- Choby BA (2009). Diagnosis and treatment of streptococcal pharyngitis. *Am Fam Physician*; 79: 383–390.
- Kenealy T, *et al.* (2013). Antibiotics for the common cold and acute purulent rhinitis. *Cochrane Database Syst Rev*; 6: CD000247.
- Lund VJ (2008). Therapeutic targets in rhinosinusitis: infection or inflammation? *Medscape J Med*; 10: 105.
- Meneghetti A, *et al.* Upper Respiratory Tract Infection. http://emedicine.medscape.com/article/302460-overview Date last updated: June 21, 2018.
- Musher DM (2003). How contagious are common respiratory tract infections? *N Engl J Med*; 348: 1256–1266.
- Poole MD, *et al.* (2005). Treatment of rhinosinusitis in the outpatient setting. *Am J Med*;118: Suppl. 7A, 45S–50S.
- Rohde G (2007). Therapeutic targets in respiratory viral infections. *Curr Med Chem*; 14: 2776–2782.

- Rohde G (2009). Drug targets in rhinoviral infections. *Infect Disord Drug Targets*; 9: 126–132.
- Rosenfeld RM, *et al.* (2007). Clinical practice guideline: adult sinusitis. *Otolaryngol Head Neck Surg*; 137: 365–377.
- Shah SA, *et al.* (2007). Evaluation of echinacea for the prevention and treatment of the common cold: a meta-analysis. *Lancet Infect Dis*; 7: 473–480.
- Tiwari T, *et al.* (2005). Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC Guidelines. *MMWR Recomm Rep*; 54: 1–16.

Pneumonia

Gernot Rohde and Mark Woodhead

Background and definitions

Pneumonia is a condition caused by microbial infection within the lung parenchyma. This infection, together with the associated host inflammatory response, impairs normal alveolar function (*i.e.* gas exchange), which, together with the systemic effects of the infection, causes the clinical features of pneumonia. The gold standard for recognition of pneumonia is the presence of new lung shadowing on a chest radiograph in the setting of a compatible clinical illness. Pneumonia is classified into groups that can be easily recognised and within which the causative pathogens, and hence the management, are different (table 1). Community-acquired pneumonia (CAP) is that which occurs in the absence of immune compromise or prior hospital admission within the previous 30–90 days.

Epidemiology

CAP occurs in between one and 10 per 1000 of the adult population each year. It is more common in children aged >5 years and becomes progressively more common from age 40 years onwards, with a peak in the very elderly. It is more common in those with comorbidity, such as COPD, bronchiectasis, and chronic cardiac or renal disease. It occurs throughout the year with a peak during the winter months.

Two types of immune dysfunction predispose to pneumonia:

- Humoral immune dysfunction, such as immunoglobulin deficiencies
- Cell-mediated immune function in, for example, cancer chemotherapy, solid organ transplantation and bone marrow transplantation

Aspiration pneumonia occurs especially in those with swallowing impairment and neurological impairment. Most cases of CAP are managed in the community with a

Key points

- Pneumonia is very common and has significant mortality.
- Severity assessment, aided by a severity assessment score, is a key management step.
- A variety of different pathogens can cause pneumonia.
- Antibiotic management is initially empirical, and based on guidelines and knowledge of local microbial patterns and resistance rates.

Table 1 Classical pneumonia triad

	Setting of acquisition	Immune status
CAP	Community	Immunocompetent
Nosocomial pneumonia	Hospital	Immunocompetent
Pneumonia in the immunocompromised host	Any	Severe immunosuppression[#]

[#]: patients are at increased risk of so-called opportunistic infections.

variable, but significant, proportion requiring hospital admission. Of those admitted, ~13% may die and of those reaching the intensive care unit, 30–50% may die.

Clinical features

The duration of illness before presentation is usually short. Classically, there is an abrupt onset of symptoms:

- respiratory symptoms such as cough with or without sputum, dyspnoea and pleuritic chest pain;
- general symptoms such as shivers and malaise, myalgia, arthralgia, headache, palpitations, and diarrhoea; or
- neurological symptoms (mainly confusion).

A slower onset over a few days may also occur.

Abnormalities on clinical examination include:

- dyspnoea indicated by increased respiratory rate
- tachycardia, low blood pressure, dullness to percussion or focal signs on chest examination, most commonly crackles and/or bronchial breathing and enhanced vocal resonance

Chest signs may, however, be absent, making the diagnosis difficult outside hospital. Particularly in elderly patients, pneumonia may present oligosymptomatically, and the presence of fever, cough or sputum may be less frequent. More frequently, confusion and diarrhoea may be the predominant symptoms in this age group.

Clinical features are generally not helpful in predicting the causative organism. Investigations, including radiology, are not systematically recommended outside hospital but, in those admitted, are performed to aid precise diagnosis, assess illness severity and identify the microbial cause. A chest radiograph is essential to confirm new lung shadowing in those admitted. Classically, such shadowing conforms to a lobar pattern and is associated with air bronchograms. More commonly, shadowing may occupy less than a whole lobe, and may also be patchy, multilobar and bilateral. Additional features may include pleural effusion and, less commonly, cavitation and pneumothorax. The lower lobes are most commonly affected.

Alternatively, chest ultrasound may support the diagnosis with a high sensitivity and specificity. However, more centrally located consolidations may be missed and a negative result does not exclude the diagnosis of pneumonia.

In routine blood tests, peripheral blood white cell count may be raised, especially in bacterial infection, but C-reactive protein and procalcitonin are probably more specific.

Blood urea and creatinine are helpful in severity assessment and the assessment of renal impairment, and liver function tests may be abnormal. Measures of gas exchange, such as oxygen saturation and/or arterial blood gases, also aid assessment of illness severity and guide management. In routine practice, tests to identify a microbial cause are positive in only about 15% of cases of CAP and hence seldom influence management. They are probably not indicated unless the patient is severely ill. In such cases, blood culture, sputum Gram stain and culture, and urine tests for pneumococcal and *Legionella* antigens are indicated. Blood antibody levels or nose/throat secretion PCR-based tests for microbe-specific nucleic acids can be used for the detection of viruses and less common bacteria such as *Legionella*, *Mycoplasma* and *Coxiella*.

The differential diagnosis of CAP includes acute bronchitis, COPD exacerbation, left ventricular failure, pulmonary embolism, TB, exacerbation of pulmonary fibrosis and rare lung disorders (*e.g.* pulmonary eosinophilia).

Microbial aetiology and resistance

The same 10 pathogens commonly cause CAP worldwide, with *Streptococcus pneumoniae* being the most common overall, and the most important cause of severe illness and death. *Mycoplasma pneumoniae* is also a common cause of mild illness, especially in young adults. Severe illness is most likely to be associated with *S. pneumoniae*, *Legionella*, staphylococcal or Gram-negative bacterial infection. *Legionella* infection may occur in outbreaks associated with a water aerosol source, such as showers or decorative fountains. Staphylococcal infection is especially common following influenza virus infection and in intravenous drug abusers. Influenza occurs in seasonal outbreaks during the winter months and occasional pandemics. It is the most common viral cause of CAP. Bacterial antibiotic resistance varies in frequency between countries. Clinically significant resistance to penicillins in *S. pneumoniae* is rare but clinically significant macrolide resistance is more common, especially in Southern Europe (www.earss.rivm.nl).

Humoral immune deficiency is associated with bacterial infection and cell-mediated immune defects with viral and fungal infections such as *Pneumocystis jirovecii*. Anaerobic bacteria may be important in aspiration pneumonia.

Severity assessment

Severity assessment aims to identify patients with increased risk of mortality in order to offer these patients intensified monitoring and therapy. This should be done through clinical judgement guided by objective severity scores. There are many of these, but the best validated for CAP are CURB65 (and its derivative CRB65) and the Pneumonia Severity Index (PSI). The latter is based on a score from 20 variables and is often not practical in routine practice. The former is simpler and based on the number of severity variables present (table 2).

This score should be complemented by:

- assessment of functional status
- clinical evaluation of potentially instable comorbidities
- measurement of oxygenation

It is important to immediately identify patients in need for intensive treatment on admission. Evaluation of organ dysfunction should be performed using the American

Table 2 CRB-65 criteria and additional parameters for risk prediction before outpatient treatment

Parameter	CRB-65 criteria	Additional parameters
Impaired consciousness	Newly arisen	
Respiratory rate	≥30 per min	
Blood pressure	<90/≤60 mmHg	
Age	≥65 years	
Comorbidities[#]		(Potentially) decompensated
Oxygen saturation		<90%
Functional status		Chronically bedridden

[#]: chronic cardiac, neurological, hepatic, renal or malignant accompanying disease.

Thoracic Society/Infectious Diseases Society of America minor criteria (table 3) and assessment of potentially instable comorbidities.

Patients in need of mechanical ventilation or vasopressor therapy (major criteria) need to be treated in the intensive care unit.

Management

Correction of gas exchange and fluid balance abnormalities, and the provision of appropriate antimicrobial therapy are the cornerstones of management. Outside hospital, rest, oral fluids and an oral antibiotic may be all that is required. In hospital, oxygen at a concentration to maintain S_{aO_2} (92–95%) should be delivered. If this cannot be achieved, CPAP may be helpful. If there is an unacceptable rise in P_{aCO_2}, then assisted ventilation should be considered. A place for NIV in pneumonia management has yet to be proven. Initial antibiotic therapy must be empirical and directed by illness severity according to national or international guidelines (table 4). Empirical antibiotics for CAP should always include pneumococcal coverage. Treatment for nosocomial

Table 3 American Thoracic Society/Infectious Diseases Society of America minor criteria

Confusion
Uraemia
Respiratory rate ≥30 breaths per min
Hypotension
P_{aO_2}/F_{IO_2} ≤250
Multilobar infiltrates
Leukopenia
Thrombocytopenia
Hypothermia

There is a high risk of need for intensive care unit treatment if more than two out of the nine criteria are present. F_{IO_2}: inspiratory oxygen fraction.

Table 4 European Respiratory Society/European Society for Clinical Microbiology and Infectious Diseases antibiotic guideline options for CAP

Outside hospital	Amoxicillin Tetracycline
Hospitalised	
Nonsevere	Aminopenicillin ± macrolide Aminopenicillin/β-lactamase inhibitor ± macrolide Non-antipseudomonal cephalosporin Cafotaxime or ceftriaxone ± macrolide Levofloxacin Moxifloxacin Penicillin G ± macrolide
Severe	
No *Pseudomonas* risk	Non-antipseudomonal cephalosporin III + macrolide Moxifloxacin or levofloxacin ± non-antipseudomonal cephalosporin III
Pseudomonas risk	Antipseudomonal cephalosporin + ciprofloxacin Antipseudomonal cephalosporin + macrolide + aminoglycoside[#] Acylureidopenicillin/β-lactamase inhibitor + ciprofloxacin Acylureidopenicillin/β-lacatamase inhibitor + macrolide + aminoglycoside[#] Carbapenem[¶] + ciprofloxacin Carbapenem[¶] + macrolide + aminoglycoside[#]

Evidence does not clearly support one regimen as better than another so a choice is provided. The decision will depend upon local circumstances. [#]: gentamicin, tobramycin or amikacin; [¶]: meropenem is preferred.

pneumonia should be guided by knowledge of local microbial causes, and that for pneumonia in immunocompromised patients by the type of immune suppression and likely pathogens. Duration of therapy is usually 5–7 days in uncomplicated cases but may need to be prolonged in severe illness. Failure to respond should prompt a re-evaluation of the correct diagnosis and a more detailed search for microbial cause (*e.g.* by bronchoscopy) as long as gas exchange function will allow.

The greatest risk of worsening of organ function is within the first 72 h after admission to the hospital. A minimum standard for all hospitalised patients is the re-evaluation of stability criteria once per day (table 5). If all these criteria are met, the risk of repeated acute organ dysfunction is low.

Prevention

The main preventable risk for pneumonia is tobacco smoking. In those with comorbid disease and in the elderly, influenza and pneumococcal vaccination are indicated. Recent evidence suggests that conjugate pneumococcal vaccination in children not only reduces invasive pneumococcal infection in this group but also in adults.

Table 5 Criteria for clinical stability

Heart rate ≤100 beats per min
Respiratory rate ≤24 breaths per min
Systolic blood pressure ≥90 mmHg
Body temperature ≤37.8°C
Ability to take food by mouth
Normal state of consciousness
No hypoxaemia (P_{O_2} ≥60 mmHg (7.98 kPa), S_{aO_2} ≥90%)

P_{O_2}: oxygen tension.

Further reading

- Kolditz M, *et al.* (2017). Community-acquired pneumonia in adults. *Dtsch Arztebl Int*; 114: 838–848.
- Lim WS, *et al.* (2000). Severity prediction rules in community acquired pneumonia: a validation study. *Thorax*; 55: 219–223.
- Pletz MW, *et al.* (2016). Advances in the prevention, management, and treatment of community-acquired pneumonia. F1000Research; 5: 300.
- Torres A, *et al.* (2006). Respiratory Infections. London, Hodder Arnold.
- Woodhead M, *et al.* (2011). Guidelines for the management of adult lower respiratory tract infections – full version. *Clin Microbiol Infect*; 17: Suppl. 6, E1–E59.

Hospital-acquired pneumonia

Francesco Blasi, Andrea Gramegna and Marta Di Pasquale

The currently proposed classification of hospital-acquired pneumonias includes hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). HAP is defined as pneumonia that occurs ≥48 h after admission that was not incubating at the time of admission. VAP is defined as pneumonia that arises >48–72 h after endotracheal intubation.

The European Respiratory Society (ERS)/European Society of Intensive Care Medicine (ESICM)/European Society of Clinical Microbiology and Infectious Diseases (ESCMID)/Latin American Thoracic Society (ALAT) and American Thoracic Society/Infectious Diseases Society of America decided to exclude healthcare-associated pneumonia (HCAP) from the latest HAP/VAP guidelines published in 2017 and 2016, respectively. Increasing evidence shows that many patients included in the HCAP definition are not at high risk for multidrug-resistant (MDR) pathogens and that the most important determinants of infections by MDR pathogens are underlying patient characteristics. Therefore, these patients are included in the community-acquired pneumonia population.

Epidemiology

The incidence of HAP is ~0.5–2.0% among all hospitalised patients and it is the second most common nosocomial infection, yet the first in terms of mortality (ranging from 30% to >70%). The incidence in different hospitals and different wards of the same hospital varies considerably. The main risk factors are:

- age
- type of hospital
- type of ward

Key points

- The incidence of hospital-acquired pneumonia is ~0.5–2%, with risk factors including age, type of hospital and type of ward.
- The mortality is high (30–70%).
- Diagnosis can be difficult, and requires a combined clinical and bacteriological approach.
- Antimicrobial therapy must be both prompt and appropriate, and should be modified as culture results become available.

Patients aged <35 years are less prone to develop HAP than elderly patients; the incidence of HAP may vary between five and 15 episodes per 1000 discharges. In large teaching hospitals, the incidence is higher than in district hospitals. This is possibly related to differences in patient complexity. HAP is quite uncommon in paediatric and obstetric wards, and clearly most common in surgical wards and intensive care units (ICUs), particularly in ventilated patients, in whom the incidence may be >35 episodes per 1000 patient-days.

Most studies on HAP have been conducted in patients hospitalised in the ICU, as mechanical ventilation represents a major risk factor for nosocomial pneumonia and specifically for VAP. However, epidemiological data seem differ between patients acquiring HAP in the ICU *versus* general wards, suggesting the importance of identifying non-ICU-acquired pneumonia as a clinical distinct entity in terms of both aetiology and management.

Pathogenesis and risk factors

Understanding of pathogenesis of HAP is fundamental to the comprehension of the risk factors involved. The main sources of HAP pathogens include:

- healthcare devices
- the environment
- the transfer of microorganisms between the patient and staff or other patients
- oropharyngeal and gastric colonisation, with subsequent aspiration of their contents into the lungs in patients with impaired mechanical, cellular and humoral defences

Risk factors for the development of HAP can be differentiated into modifiable and nonmodifiable conditions. Modifiable conditions can be classified as follows.

- Host related: adequate nutrition, reduction/discontinuation of immunosuppressive treatments, prevention of unplanned extubation, incentive spirometry, deep breathing and pain control
- Device/treatment related: minimise use of sedatives and paralytics, avoid gastric overdistention, avoid intubation and reintubation, semirecumbent positioning, drain condensate from ventilator circuits, continuous aspiration of subglottic secretions
- Environment related: attention to infection-control procedures, *i.e.* staff education, hand washing, patient isolation, microbiological surveillance programme

Microbiology

Gram-negative bacterial pathogens are the main cause of HAP: *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, microorganisms belonging to the family Enterobacteriaceae (*Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., *etc.*) and under certain conditions, microorganisms such as *Haemophilus influenzae* are also involved in HAP aetiology. Among Gram-positive pathogens, *Staphylococcus aureus* (both methicillin-sensitive *S. aureus* and methicillin-resistant *S. aureus* (MRSA)) and *Streptococcus* spp. are the most common agents, accounting for 35–39% of all cases. Nonbacterial pathogens such as *Aspergillus* spp. and viruses (cytomegalovirus) have been described.

In general, there are significant geographical differences in the rates of resistance between European areas and even within countries, from one hospital to another.

Table 1. Risk factors for MDR pathogens

MDR VAP	Prior intravenous antibiotic use within 90 days Septic shock at time of VAP ARDS preceding VAP ≥5 days of hospitalisation prior to the occurrence of VAP Acute renal replacement therapy prior to VAP onset
MDR HAP	Prior intravenous antibiotic use within 90 days
MRSA VAP/HAP	Prior intravenous antibiotic use within 90 days
MDR *Pseudomonas* VAP/HAP	Prior intravenous antibiotic use within 90 days

ARDS: acute respiratory distress syndrome.

The time of onset of nosocomial pneumonia also affects the possible aetiology, empirical antimicrobial treatment and outcomes. Previously, the expected pathogens for late onset of VAP/HAP (>4 days after hospital admission) were MDR. Recently, some investigators have found comparable aetiologies in patients with early- or late-onset VAP/HAP. These findings could represent the worldwide rise in MDR pathogens, underpinning that the local ICU/ward ecology is the most important risk factor for acquiring MDR pathogens. The initial HAP or VAP severity is also a strong risk factor for MDR pathogens, regardless of time of onset. Table 1 shows risk factors for MDR pathogens.

Diagnostic strategy

The clinical diagnosis of HAP is often difficult to establish. European and American guidelines suggest the use of a combined clinical and bacteriological strategy.

In cases of doubt or relevant disagreement between the clinical presentation and the radiological findings, it is recommended to perform CT. The presence of new chest

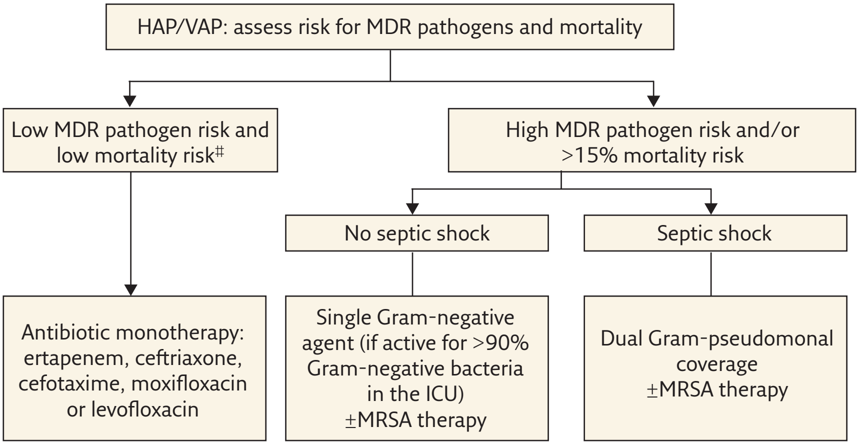

HAP/VAP: assess risk for MDR pathogens and mortality
Low MDR pathogen risk and low mortality risk#
High MDR pathogen risk and/or >15% mortality risk
No septic shock
Septic shock
Antibiotic monotherapy: ertapenem, ceftriaxone, cefotaxime, moxifloxacin or levofloxacin
Single Gram-negative agent (if active for >90% Gram-negative bacteria in the ICU) ±MRSA therapy
Dual Gram-pseudomonal coverage ±MRSA therapy

Figure 1. Empiric antibiotic treatment algorithm for HAP/VAP. #: low risk for mortality is defined as a ≤15% chance of dying, a mortality rate that has been associated with better outcome using monotherapy than combination therapy when treating serious infection. Reproduced from Torres et al. (2017).

Table 2. Summary of treatment guidelines

	Recommended treatment options	Recommended dosages
Low MDR pathogen risk and low mortality risk (≤15% chance of dying)	Aminopenicillin plus β-lactamase inhibitor or second-generation cephalosporin or respiratory fluoroquinolone	Amoxicillin–clavulanate 3 × 2.2 g Ampicillin sulbactam 3 × 3 g Cefotaxime 3 × 2 g Ceftriaxone 1 × 2 g Levofloxacin 1 × 750 mg Moxifloxacin 1 × 400 mg
High MDR pathogen risk and/or high mortality risk (>15% chance of dying) No septic shock	Anti-*Pseudomonas* β-lactams or carbapenems or fluoroquinolone	Piperacillin/tazobactam 3 × 4.5 g Ceftazidime 3 × 2 g Cefepime 2 × 2 g Imipenem 3 × 1 g Meropenem 3 × 1 g Ciprofloxacin 3 × 400 mg Levofloxacin 1 × 750 mg
	Addition of coverage for MRSA if suspected	Vancomycin 2 × 1 g Linezolid 2 × 600 mg
With septic shock	Anti-*Pseudomonas* β-lactams or carbapenems	Piperacillin/tazobactam 3 × 4.5 g Ceftazidime 3 × 2 g Cefepime 2 × 2 g Imipenem 3 × 1 g Meropenem 3 × 1 g
	plus aminoglycoside	Amikacin 1 × 15–20 mg·kg^{-1} Gentamicin 1 × 5–7 mg·kg^{-1} Tobramycin 1 × 5–7 mg·kg^{-1}
	or fluoroquinolone	Ciprofloxacin 3 × 400 mg Levofloxacin 1 × 750 mg
	or if *Acinetobacter* is a possible pathogen	Colistin 2 × 2.5 mg × (1.5 × CrCl + 30)
	Addition of coverage for MRSA if suspected	Vancomycin 2 × 1 g Linezolid 2 × 600 mg

CrCl: creatinine clearance.

radiographic infiltrates plus one of the fever >38°C, leukocytosis or leukopenia and purulent secretions is sufficient to start antimicrobial treatment.

As both HAP and VAP have high mortality and high health costs, it is compelling to try to determine microbial aetiology using invasive techniques to obtain samples (*e.g.* bronchoalveolar lavage or pleural fluid) besides standard samples (sputum, tracheal aspirate, serology, urinary antigens and blood cultures).

Treatment

Prompt administration of appropriate antimicrobial treatment is crucial to achieve an optimal outcome. Inappropriate antimicrobial treatment is associated with an excess of mortality attributable to pneumonia. Antibiotic selection for empirical therapy of HAP should be based primarily on the risk of MDR pathogen infection and mortality risk, in addition to local antibiotic-resistance data. Figure 1 shows the proposed empirical treatment approach from the latest ERS/ESICM/ESCMID/ALAT guidelines.

Once the results of respiratory tract and blood cultures become available, therapy should be focused or narrowed based on the isolation of specific pathogens and their susceptibility to single antimicrobials. A 7–8-day antibiotic course can be appropriate provided that the patient has a good clinical response and difficult-to-treat pathogens are not involved as aetiological agents.

For patients with VAP due to Gram-negative bacilli that are susceptible to only aminoglycosides or polymyxins (colistin or polymyxin B), attempts have been made to combine inhaled and systemic antibiotics rather than using systemic antibiotics alone. Unfortunately, the available study on the topic, as IASIS Trial published in 2017, showed no efficacy in improving clinical outcomes despite reducing bacterial burden. Therefore, there is still no consensus on the use of inhaled antibiotics in VAP.

In recent years, the increasing identification of difficult-to-treat pathogens has led to a higher mortality rate. Therefore, new molecules have been studied and tested. Several promising compounds are becoming available against MDR bacteria, especially against MRSA and Gram-negative extended-spectrum β-lactamase bacteria, such as tedizolid (a new oxazolidine), iclaprim (a novel drug related to trimethoprim), plazomicin (a new aminoglycoside) and two combinations (ceftazidime/avibactam and ceftolozane/tazobactam).

Figure 1 and table 2 summarise current treatment guidelines.

Further reading

- Di Pasquale M, *et al.* (2016). Non-intensive care unit acquired pneumonia: a new clinical entity? *Int J Mol Sci*; 17: 287.
- Liapikou A, *et al.* (2016). Emerging drugs for nosocomial pneumonia. *Expert Opin Emerg Dr*; 21: 331–341.
- Kalil AC, *et al.* (2016). Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*; 63: e61–e111.
- Ramirez P, *et al.* (2012). Measures to prevent nosocomial infections during mechanical ventilation. *Curr Opin Crit Care*; 18: 86–92.
- Torres A, *et al.* (2009). Defining, treating and preventing hospital acquired pneumonia: European perspective. *Intensive Care Med*; 35: 9–29.
- Torres A, *et al.* (2010). Treatment guidelines and outcomes of hospital-acquired and ventilator-associated pneumonia. *Clin Infect Dis*; 51: Suppl. 1, S48–S53.
- Torres A, *et al.* (2017). International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. *Eur Respir J*; 50: 1700582.

Pneumonia in the immunocompromised host

Santiago Ewig

In contrast to community- and hospital-acquired pneumonia, pneumonia in the immunocompromised host is not defined by the setting of pneumonia acquisition but by the immune status of the host. In this context, immune suppression is best defined as a relevant risk for so-called opportunistic pathogens such as fungi, viruses, mycobacteria and parasites.

The expected pathogen patterns differ according to the type of immunosuppression (table 1). Overall, there are six main types of immunosuppression:

- Iatrogenic (through steroidal and nonsteroidal agents);
- Neutropenia (usually through antineoplastic chemotherapy);
- Haematopoietic stem-cell transplantation (HSCT);
- Solid-organ transplantation;
- Uncontrolled HIV infection;
- Innate or acquired T- and B-cell deficiencies.

Each immunosuppressive condition confers characteristic risk profiles for pulmonary infections according to the type of immune failure. Some conditions additionally show time- or extent-dependent risk profiles. Several additional factors such as age, comorbidity, functional status and co-infections impact immune responses and result in a so-called 'net state of immunosuppression'.

It should be stressed that in addition to opportunistic pathogens, patients with immunosuppression are at increased risk to ordinary community- and nosocomially acquired pathogens as well. This is particularly true for bacteria and respiratory viruses (influenza, parainfluenza, respiratory syncytial virus and adenovirus, among others).

Key points

- Different types of immunosuppression confer particular vulnerability to different respiratory pathogens, which may be bacterial, viral, mycobacterial or fungal.
- The approach to treatment should include comprehensive diagnostic evaluation, indications for empirical antimicrobial treatment and an approach in case of treatment failure.

Table 1. Types of immunosuppression and typical infectious complications

Type of complication	Main immune disorder	Typical infections
Iatrogenic (steroids)	Macrophages, T-cells	Bacteria, fungi (*Pneumocystis jirovecii*, *Aspergillus* spp.), *Mycobacterium tuberculosis*
Iatrogenic (anti-TNF-α)	TNF-α	*Mycobacterium tuberculosis*
Neutropenia, HSCT	Neutrophils	
	Short duration (<10 days)	Bacteria
	Long duration (>10 days)	Additionally: fungi (*Aspergillus* spp.)
Solid-organ transplantation	Early (month 1): neutrophils	Bacteria
	Intermediate (months 2–6): macrophages, T-cells	Fungi, viruses, parasites
	Late (months >6): depends on extent of immune suppression	Variable
HIV infection	$CD4^+$ T-cell count >500 cells · μL^{-1}	No risk
	$CD4^+$ T-cell count 200–500 cells · μL^{-1}	Bacteria, *Mycobacterium tuberculosis*
	$CD4^+$ T-cell count <200 cells · μL^{-1}	Additionally: *Pneumocystis jirovecii*
	$CD4^+$ T-cell count <50 cells · μL^{-1}	Additionally: *Aspergillus* spp., atypical mycobacteria

Pulmonary infections in the immunocompromised host usually constitute an emergency. Thus, immediate appropriate antimicrobial treatment is mandatory. Since the spectrum of potential pathogens is far more diverse than in immunocompetent hosts, a systematic approach to the management of these patients is required. This approach should include a comprehensive diagnostic evaluation, indications for empirical initial antimicrobial treatment, in the absence of definite pathogen identification, and for management in case of treatment failure.

The basic diagnostic evaluation should include history, physical examination and chest radiography as well as a basic microbiological work-up (sputum and blood cultures). A CT scan of the lung (multi-slice scan and HRCT) is usually indicated in patients in whom a straightforward diagnosis cannot be made. It can be particularly valuable in patients at risk of fungi (*Pneumocystis* and *Aspergillus*). Bronchoscopy is usually indicated in patients with bilateral infiltrates, unusual clinical and radiographic presentations, or treatment failure. When performing bronchoscopy, particular care has to be taken to comply with the methodology of retrieving uncontaminated samples of the lower respiratory tract, adequate processing and a comprehensive evaluation of the samples retrieved. Bronchoalveolar lavage (BAL) is the most important sample, and stains and cultures should be investigated for all relevant pathogens. Occasionally, transbronchial biopsies and/or transbronchial needle biopsies of thoracic lymph nodes may be rewarding. Additional options include CT-guided and video-assisted thoracoscopic surgery biopsies.

Pneumocystis jirovecii pneumonia

P. jirovecii pneumonia in HIV-infected patients usually occurs in patients with <200 CD4$^+$ helper T-cells per microlitre. It presents with at least one of the following symptoms: fever, cough and dyspnoea on exertion; oral candidiasis is virtually always present. Chest radiography typically discloses bilateral interstitial infiltrates in a perihilar distribution but may also be normal in the early course. In the latter case, HRCT may reveal ground-glass opacities in a patchy or geographical distribution. Atypical cystic presentations may occur. Blood gas analysis shows wide alveolar–arterial gradients. The typical but nonspecific laboratory finding is an elevated lactate dehydrogenase level. Specific diagnosis is required and may be established by examination of induced sputum or BAL. The treatment of choice (also for prophylaxis) is timethoprim-sulfamethoxazole. Second-line options include pentamidine and clindamycin/primaquine. Adjunctive steroids are indicated in patients with acute respiratory failure.

P. jirovecii pneumonia in non-HIV patients differs in that it presents more frequently as an acute-onset pneumonia and tends to be associated with higher mortality.

Cytomegalovirus pneumonia

Cytomegalovirus (CMV) pneumonia is defined as pulmonary signs and symptoms and the detection of CMV in pulmonary samples. Nevertheless, patients may shed CMV in the absence of CMV pneumonia. Co-infections with other opportunistic pathogens are frequently encountered. After introduction of CMV prophylaxis, the incidence in allogeneic HSCT is 10–30%, with the highest risk in seropositive recipients, while it is rare in autologous HSCT (<10%). In addition, the onset is shifted to >100 days. Clinical presentation is unspecific. Radiologically, there is typically an interstitial pattern with tiny pulmonary nodules and patchy areas of consolidation. HRCT is more sensitive. Diagnosis is made by demonstration of inclusion bodies within epithelial cells of the lower respiratory tract (sensitivity 90%, specificity 98%). Culture of BAL fluid, PCR and pp65 antigen indicate CMV replication but all lack specificity. DNA-quantification in BAL is currently the best method to establish a diagnosis of CMV pneumonia. For a long time, the treatment of choice has been ganciclovir and valganciclovir, combined with CMV immunoglobulin. Recently, letermovir has been introduced for prophylaxis; it is less toxic and is also active against strains resistant to other antiviral agents and carries high promise for treatment as well. Second-line agents are foscarnet and cidofivir. Antiviral prophylaxis and monitoring are the main preventive strategies.

Tuberculosis

Patients with reduced CD4$^+$ cell counts, and those on chronic steroid and anti-tumour necrosis factor (TNF)-α treatment are at increased risk of TB. Co-infection with TB and HIV alters the natural history of both diseases. TB in HIV-infected patients presents like primary infection (patchy infiltrates, mediastinal lymph node enlargement, pleural effusion and bacteraemia). Anti-TB treatment of pulmonary TB follows the rules of standard treatment; *i.e.* usually a 2-month regimen consisting of four first-line drugs (isoniazid, rifampicin, ethambutol and pyrazinamide) followed by a 4-month regimen consisting of two drugs (isoniazid and rifampicin). Testing for drug susceptibility is mandatory and treatment must usually be modified in the presence of resistance. Concurrent treatment of TB and HIV is challenging due to the many complex interactions of anti-TB drugs and antiretroviral agents. Patients who are candidates for chronic steroid or anti-TNF-α treatment should be evaluated for TB infection and, in the case of positive skin testing or interferon-γ release assay, receive prophylaxis.

Table 2. Diagnostic criteria for invasive aspergillosis

Definitive	Histological proof or positive culture from otherwise sterile site
Probable	Host factor + typical CT and/or tracheobronchitis + mycological criteria
Possible	Host factor + CT and/or tracheobronchitis

Host factors: several conditions associated with severe immunosuppression; CT: typical (albeit not specific) CT signs (*e.g.* the halo sign); tracheobronchitis: bronchoscopic visualisation of typical pseudomembranes on the tracheal mucosa (maybe subject to biopsy proof); mycological criteria: *e.g.* culture positive for *Aspergillus*, or positive galactomannan test in serum or BAL fluid. Information from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group.

Aspergillus pneumonia and other fungal pathogens

Definite diagnosis of *Aspergillus* pneumonia in neutropenic patients requires tissue biopsy and can only rarely be established. Therefore, probable and possible diagnosis is based on a set of clinical, microbiological and radiographic criteria (table 2). HRCT is the method of choice to detect *Aspergillus* pneumonia early in its course. Typical, albeit not specific, signs of *Aspergillus* pneumonia include the 'halo' sign, as well as nodular and peripheral patchy densities near to vessels. The 'air crescent' sign, representing cavitation, is a late marker of *Aspergillus* pneumonia. The galactomannan antigen test in serum and BAL has a sensitivity of ~70% and a specificity of 90%. Bronchoscopy is usually indicated. Early initiation of treatment is crucial. The treatment of choice for definite *Aspergillus* pneumonia is voriconazole or, alternatively, liposomal amphotericin B. Second-line options include caspofungin and posaconazole. In some centres, isavuconazole is used as first-line treatment. In any case, treatment must be adjusted to previous prophylaxis; patients on posaconazole prophylaxis should receive liposomal amphotericin B or caspofungin. Mortality depends on early diagnosis; it still reaches 50–60%.

Since the introduction of prophylaxis against *Aspergillus*, other important fungi have emerged, predominantly including mucorales and fusarium spp. Treatment options for mucorales include liposomal amphotericin B, posaconazole and isavuconazole, and for fusarium include liposomal amphotericin B and voriconazole.

Further reading

- Agusti C, *et al.* (2009). Pulmonary infection in the immunocompromised patient. Strategies for management. Oxford, Wiley-Blackwell.
- Benito N, *et al.* (2012). Pulmonary infections in HIV-infected patients: an update in the 21st century. *Eur Respir J*; 39: 730–745.
- Boersma WG, *et al.* (2007). Bronchoscopic diagnosis of pulmonary infiltrates in granulocytopenic patients with hematologic malignancies: BAL *versus* PSB and PBAL. *Respir Med*; 101: 317–325.
- Brownback KR, *et al.* (2014). Role of bronchoalveolar lavage in the diagnosis of pulmonary infiltrates in immunocompromised patients. *Curr Opin Infect Dis*; 27: 322–338.
- Duncan MD, *et al.* (2005). Transplant-related immunosuppression: a review of immunosuppression and pulmonary infections. *Proc Am Thorac Soc*; 2: 449–455.

- Fishman JA, *et al.* (1998). Infection in organ-transplant recipients. *N Engl J Med*; 338: 1741–1751.
- Hamblin AD, *et al.* (2008). The immunodeficiency of chronic lymphocytic leukaemia. *Br Med Bull*; 87: 49–62.
- Maschmeyer G, *et al.* (2015). Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients (allogeneic SCT excluded): updated guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). *Ann Oncol*; 26: 21–33.
- Rañó A, *et al.* (2001). Pulmonary infiltrates in non-HIV immunocompromised patients: a diagnostic approach using non-invasive and bronchoscopic procedures. *Thorax*; 56: 379–387.
- Roifman CM, *et al.* (2013). Primary T-cell immundeficiencies. *In*: Rich R, *et al.*, eds. Clinical immunology. Principles and practice. 4th Edn. Philadelphia, Elsevier Saunders; pp. 437–453.
- Schroeder HW, *et al.* (2013). Primary antibody deficiencies. *In*: Rich R, *et al.*, eds. Clinical immunology. Principles and practice. 4th Edn. Philadelphia, Elsevier Saunders; pp. 421–436.
- Ullmann AJ, *et al.* (2016). Infectious diseases in allogeneic haematopoietic stem cell transplantation: prevention and prophylaxis strategy guidelines 2016. *Ann Hematol*; 95: 1435–1455.

Influenza, pandemics and SARS

Wei Shen Lim

Seasonal and pandemic influenza

Virology

Influenza viruses are RNA orthomyxoviruses with three main types, A, B and C. Viral surface proteins include haemagglutinin (H) and neuraminidase (N) which are involved in viral attachment and release, respectively. There are 16 haemagglutinin (H1 to H16) and nine neuraminidase types (N1 to N9). Influenza A viruses are described in a standardised manner according to their type/location of first isolate/laboratory strain number/year of isolate/H and N subtypes, for example: influenza A/Hong Kong/1/68/H3N2 (the cause of the 1968 'Hong Kong' pandemic).

The natural reservoir hosts of all influenza A virus subtypes are water birds. Host specificity of influenza A virus subtypes is partially determined by the binding affinity of haemagglutinin to sialic acid residues on the host cell.

A notable feature of influenza A viruses is their propensity to undergo antigenic variation. Small alterations (antigenic drift) occur each year while large alterations (antigenic shift) are associated with pandemics.

Key points

- Influenza is mostly a self-limiting viral upper respiratory tract infection that is managed in the community. Pneumonia is the most frequent serious complication of influenza.
- Neuraminidase inhibitors, such as oseltamivir and zanamivir, are effective in the prophylaxis and treatment of influenza A infection.
- The 1918 influenza A/H1N1 pandemic was the deadliest pandemic of the 20th century, causing 40–100 million deaths worldwide.
- Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) are caused by coronaviruses.
- Nosocomial transmission resulting in large hospital outbreaks are an important feature of MERS and SARS. Early diagnosis and strong infection control measures are critical.
- The management of MERS and SARS is primarily supportive.

Seasonal influenza

Since 2009, influenza A/H1N1 pdm09 and A/H3N2 have been the main influenza virus subtypes causing seasonal influenza. Influenza B viruses, either of the Victoria or Yamagata antigenic lineages, contribute to a lesser extent. In temperate countries, seasonal influenza occurs fairly predictably over 2–4 months during winter, spreading rapidly with an average reproductive number of 1.28 and an attack rate of 10–20%; rates are highest in young children and the elderly. According to the World Health Organization, annually there are 1 billion cases of influenza, 3–5 million cases of severe illness and 300 000–500 000 deaths worldwide.

Influenza is highly transmissible. Human-to-human transmission occurs through large droplet spread and direct contact with secretions (or fomites). There is also evidence supporting aerosol transmission although the extent and importance of this is debated.

Influenza is mostly a self-limiting viral upper respiratory tract infection that is managed in the community. The mean incubation period is 2–4 days with a range of up to 7 days. An abrupt onset of high fever (up to 41°C) is the main presenting feature. The fever peaks within the first 24 h of illness and usually lasts for 3 days. Cough is the next commonest symptom (85%) which may be associated with sputum production in up to 40% of cases. Malaise (80%), chills (70%), headaches (65%) and myalgia (50%) may be prominent. Coryza and sore throat are reported in about half of patients. Children may present with vomiting, diarrhoea and abdominal pain but these symptoms are uncommon in adults. The mean duration of symptoms is 4 days.

Complications of influenza

Some patient groups experience significant morbidity and mortality. Persons at risk of complications from influenza include pregnant women, the frail elderly, those who are immunosuppressed and those with chronic medical conditions or morbid obesity.

Pneumonia is the most frequent serious complications of influenza. Two main clinical patterns are described; primary viral pneumonia and secondary bacterial pneumonia.

Patients with primary viral pneumonia typically become breathless within the first few days of onset of fever. This may be associated with tachypnoea, cyanosis and bilateral lung crackles on chest examination. Leukocytosis is usual. The commonest chest radiographic abnormality is diffuse bilateral interstitial infiltrates similar to pulmonary congestion. Progression to respiratory failure is well-recognised. Mortality rates of between 6% to 40% have been reported. In severe cases, pathologic findings are similar to those seen in acute respiratory distress syndrome.

Patients with secondary bacterial pneumonia complicating influenza typically experience an amelioration of the initial symptoms of viral infection. However, 4–10 days later, experience a recurrence of fever together with breathlessness and a productive cough ensues. Clinical features at this point are indistinguishable from community-acquired bacterial pneumonia. The commonest pathogens implicated are *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* and *Streptococcus* sp. In children, the commonest respiratory complication, though not the most serious, is otitis media.

In addition to the specific complications listed in table 1, patients with influenza may also experience a worsening of a pre-existing medical illness such as COPD or cardiac failure.

Table 1. Complications of influenza in adults and children

Complication	Incidence	
	Adults	Children
Otitis media	Common	Very common
Secondary bacterial pneumonia	Common	Uncommon
Primary viral pneumonia	Common	Uncommon
Myositis	Uncommon	Rare
Myocarditis	Rare	Rare
Encephalitis/encephalopathy	Rare	Rare
Reye's syndrome		Rare
Febrile convulsions		Common

Diagnosis

Reverse-transcriptase (RT)-PCR performed on respiratory samples (such as nose and throat swabs or nasopharyngeal aspirates) is the most sensitive and specific mode of diagnosis. Immnoassays that detect influenza viral nucleoprotein antigens are also commonly used, but are generally less sensitive than RT-PCR. Viral culture is seldom used for clinical management while serological testing provides a retrospective diagnosis.

Treatment

There are two main classes of drugs licensed for the treatment of influenza. The use of M2 ion channel inhibitors, such as amantadine and rimantadine, is limited because of widespread resistance to these drugs amongst prevailing seasonal influenza viruses. Neuraminidase inhibitors (NAIs), such as oseltamivir, zanamivir, peramivir and laninamivir, are the current agents of choice against influenza A and B viruses. Oseltamivir is the most widely used NAI because of ease of administration (oral *versus* inhaled/intravenous) though nausea is a common side-effect (OR 1.79, 95% CI 1.10–2.93).

Greatest benefit is derived when antiviral treatment is started within 48 h of symptom onset. A 2014 Cochrane meta-analysis of randomised placebo-controlled trials found that oseltamivir reduced the time to first alleviation of symptoms in adults by 0.7 days and zanamivir by 0.6 days; in these trials, most patients were treated in the community and NAIs did not significantly reduce hospitalisations. In contrast, large cohort studies, including an individual-patient data meta-analyses of NAI use mainly during the 2009 pandemic, suggest that antiviral treatment is associated with reduced mortality (OR 0.81, 95% CI 0.70–0.93).

Adjuvant corticosteroids in severe influenza is not routinely advocated based on current data; a Cochrane meta-analysis of observational cohort studies suggested increased harm (OR 3.06, 95% CI 1.58–5.92), though most studies were of very low quality and confounding by indication was a major concern. For patients with influenza-associated pneumonia, antibiotics are usually advised in view of the risk of secondary bacterial infections.

Chemoprophylaxis and vaccination

Both oseltamivir and zanamivir taken as prophylactic agents reduce the chance of symptomatic laboratory-confirmed influenza (the number needed to treat to benefit: n=33 to 51).

Immunisation is the backbone of influenza prevention. The relative protective efficacy in children and young healthy adults is broadly 70% to >90%. Trivalent influenza vaccines (containing components to A/H1N1pdm009, A/H3N2 and one influenza B-like virus) are gradually being replaced by quadrivalent vaccines (containing components to both influenza B virus lineages). Newer vaccines, such as those containing higher doses of antigenic component or conjugated vaccines, are more immunogenic and are felt to provide increased levels of protection for individuals in whom protective efficacy with older inactivated vaccines has been lower (40%), such as the elderly. There are few head-to-head trials comparing vaccine effectiveness between vaccines. In many countries, annual influenza vaccination of susceptible individuals and healthcare workers is considered cost-effective.

Neuraminidase inhibitor resistance

Viruses carrying a histidine to tyrosine mutation at residue 275 of the neuraminidase protein (H275Y) exhibit reduced susceptibility (>100-fold) to oseltamivir and peramivir but remain susceptible to zanamivir and laminamivir. Amino acid changes in residue 222 (I222R) confer a 10–100-fold reduced susceptibility to oseltamivir. Combined I222R and H274Y mutations lead to cross-resistance to all four currently licensed NAIs. Fortunately, among prevailing influenza viruses, drug-resistant isolates remain infrequent.

Pandemic influenza

A pandemic may be simply defined as the worldwide spread of a new disease. An influenza pandemic manifests as: 1) the appearance of a novel influenza antigenic type; 2) that causes severe human infection; and 3) which spreads easily from human-to-human. Only influenza A viruses have been associated with influenza pandemics.

In the 20th century, influenza pandemics occurred in 1918 (H1N1), 1957 (H2N2), 1968 (H3N2) and 2009 (H1N1) (figure 1). Each of these pandemics had a different impact and tempo. The 1918 pandemic was the deadliest, claiming the lives of an estimated 1–3% of the global population at the time (table 2); a high mortality amongst healthy individuals aged 20–40 years was a unique feature of the pandemic. The 2009 pandemic was the least severe; older persons aged >60 years were relatively protected due to pre-existing cross-reactive antibodies from previous exposure to antigenically similar influenza viruses.

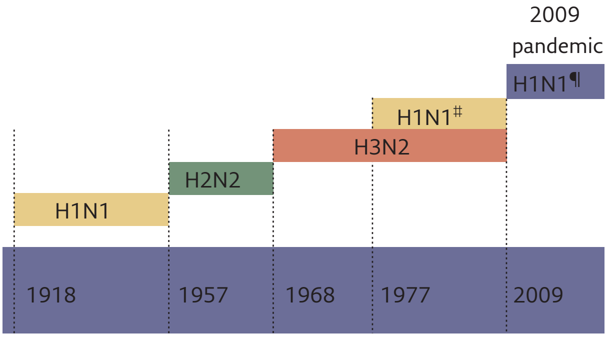


Figure 1. Influenza pandemics and subtypes, 1918–2009. #: re-emergence of H1N1, possibly from accidental laboratory release – strain closely related to 1950 strain. ¶: new reassortment of six gene segments from triple-reassortant North American swine influenza virus lineages and two gene segments from Eurasian swine influenza virus lineages.

Table 2. Influenza pandemics in the 20th century

Year	Influenza subtype	Global estimated mortality
2009	H1N1pdm09	150 000–580 000
1968	H3N2	1 million
1957	H2N2	1 million
1918	H1N1	40–100 million

Threats from new avian influenza viruses

Over the past two decades, there have been a number of outbreaks of human infection due to emerging avian influenza viruses. Since 2003 to June 2018, avian influenza A(H5N1) has caused 860 cases in 16 countries, with 454 deaths. From 2013 to June 2018, avian influenza A(H7N9) caused 1567 cases with 615 deaths over six waves, with the vast majority of cases occurring in China. Human infections have also occurred due to avian influenza A(H5N6), A(H9N2) and A(H7N4) viruses. Avian influenza A(H7N9) is considered to be the highest potential pandemic risk.

Severe acute respiratory syndrome and Middle East respiratory syndrome

Epidemiology

The first human case of severe acute respiratory syndrome (SARS) was identified in the city of Foshan (Guangdong Province, China) on November 16, 2002 and the last known case of the initial outbreak experienced the onset of symptoms on June 15, 2003 in Taiwan. In total, the global outbreak affected 8096 individuals in 29 countries, 774 of whom died (case fatality rate 9.5%). The three most severely affected regions were mainland China, Hong Kong and Taiwan with 5327, 1755 and 674 cases, respectively. The SARS coronavirus (SARS-CoV) was identified as the causative agent of SARS in April 2003.

The first reported case of Middle East respiratory syndrome (MERS) was a patient who died in hospital in Jeddah, Saudi Arabia in June 2012. From 2012 to June 2018, there were 2207 cases of MERS reported to the World Health Organization with 787 deaths (case fatality rate 36%). Cases have been reported from 27 countries. All cases outside the Middle East report a history of travel to the Arabian peninsula or close contact with a primary case. The MERS coronavirus (MERS-CoV) is similar to SARS-CoV.

Virology and transmission

Coronaviruses are large, single-stranded RNA viruses. They exhibit high rates of mutation and recombination with a tendency to cross host species. Bats are the natural reservoir for coronaviruses and in the 2003 SARS outbreak, market animals such as the palm civet cat (*Paguma larvata*) were the animal sources of zoonotic transmission (figure 2).

The exact source and mode of transmission of MERS-CoV to humans has been more difficult to define. Dromedary camels (*Camelus dromedarius*) appear to be the main intermediary animal reservoirs of MERS-CoV based on epidemiological, genetic and exposure linkages. However, evidence to link bats as the original source is weak. Transmission from camels to humans likely occurs *via* direct contact with camels (respiratory droplets) or through consumption of camel products (camel milk or undercooked meat).

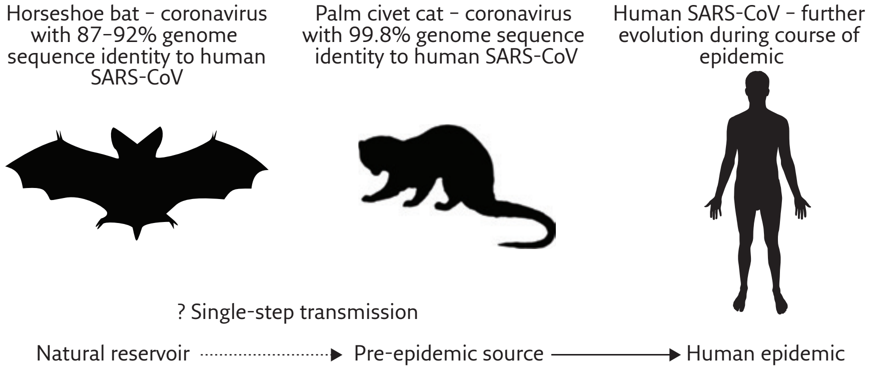

Horseshoe bat – coronavirus with 87–92% genome sequence identity to human SARS-CoV
Palm civet cat – coronavirus with 99.8% genome sequence identity to human SARS-CoV
Human SARS-CoV – further evolution during course of epidemic
? Single-step transmission
Natural reservoir
Pre-epidemic source
Human epidemic

Figure 2. Possible origin of SARS based on phylogenetic studies.

Nosocomial transmission is particularly important for both MERS and SARS; 44–100% of MERS cases in individual outbreaks were linked to hospitals. One South Korean traveller returning from the Arabian peninsula was associated with 181 infected cases of MERS through hospital contacts. Similarly, in one SARS ‘super-spreading event’ at the Prince of Wales Hospital, Hong Kong, a single patient infected 143 people. In contrast, human-to-human community transmission rates are much lower.

Clinical features

The clinical spectrum of disease for both MERS and SARS includes asymptomatic infection, a mild nonspecific respiratory illness, through to severe pneumonia. Presenting features are often nonspecific, comprising fever, chills, cough and dyspnoea. Gastrointestinal symptoms are present in about one-third of cases. Comorbid illnesses are more common in patients with MERS compared to SARS, and are a risk factor for more severe disease (table 3). Lymphopenia is recognised and extent of radiological abnormality (mainly consolidation) correlates with severity of illness and prognosis.

Diagnosis

SARS-CoV and MER-CoV are detectable by RT-PCR from respiratory tract, serum, faecal and urine samples. Serological testing allows for retrospective diagnosis.

Clinical management

The management of SARS and MERS is chiefly supportive. Although numerous compounds with activity against coronaviruses have been identified, no specific drug treatment exist. Corticosteroids, human monoclonal neutralising antibodies and convalescent sera have been tried, but clinical trials are lacking.

Table 3. Comparative features of SARS and MERS

	SARS	MERS
Basic reproduction number	>1	<1
Incubation period	5 (2–14) days	5 (2–14) days
Median time from onset to respiratory failure	11 days	7 days
Comorbid illnesses	<30%	70%
Crude fatality rate	10%	40%

Strong infection control measures are the cornerstone of containment and critical to avoid large nosocomial outbreaks.

Practice points regarding the clinical diagnosis of influenza or SARS

The early symptoms in influenza, SARS and MERS are nonspecific, primarily comprising of a fever in association with respiratory symptoms such as cough and systemic symptoms such as malaise or chills. A clinical diagnosis of influenza, SARS or MERS is therefore crucially dependent on epidemiological features. In the case of influenza, an influenza-like illness in the setting of local or community circulation of influenza viruses (*e.g.* during an influenza season) greatly increases the likelihood that the illness is due to influenza. The positive predictive value of an influenza-like illness for laboratory-confirmed influenza can range from 20–70%. Alternative pathogens to consider in instances of an influenza-like illness include parainfluenza virus, adenovirus, rhinovirus, *Mycoplasma pneumoniae* and even *Streptococcus pneumoniae*. In the diagnosis of MERS, a good travel history is crucial as is the identification of possible exposure to likely animal sources.

Further reading

- Belongia EA, *et al.* (2016). Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. *Lancet Infect Dis*; 16: 942–951.
- de Wit E, *et al.* (2016). SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol*; 14: 523–534.
- Fineberg HV (2014). Pandemic preparedness and response – lessons from the H1N1 influenza of 2009. *N Engl J Med*; 370: 1335–1342.
- Iuliano AD, *et al.* (2018). Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet*; 391: 1285–1300.
- Jefferson T, *et al.* (2014). Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev*; 4: CD008965.
- Muthuri SG, *et al.* (2014). Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *Lancet Respir Med*; 2: 395–404.
- Peiris JS, *et al.* (2003). The severe acute respiratory syndrome. *N Engl J Med*; 349: 2431–2441.
- Rodrigo C, *et al.* (2016). Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev*; 3: CD010406.
- Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, *et al.* (2010). Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. *N Engl J Med*; 362: 1708–1719.

Opportunistic infections in the immunocompromised host

Thomas Fuehner, Diana Ernst, Mark Greer, Jens Gottlieb and Tobias Welte

Immunodeficiency is the overarching term used to describe any malfunction of the immune system. In the overwhelming majority of cases, immunodeficiency is acquired as a result of medical treatment or a chronic disease such as untreated HIV infection. Solid organ transplantation has emerged in the past two to three decades as a major contributor to the prevalence of opportunistic infections. Primary immunodeficiencies encompass over 230 different rare inherited disorders, arising from genetic mutations that affect production of immune-active proteins. Regardless of their aetiology, immunodeficiencies predispose individuals to frequent infections, which may involve unusual microorganisms or demonstrate unusually severe or prolonged clinical courses. Unsurprisingly, pulmonary disease is common in immunodeficiencies, manifesting as infection, bronchiectasis with or without primary ciliary dyskinesia (PCD), inflammatory dysregulation and even malignancy.

Primary immunodeficiency

Primary immunodeficiencies (PID) are rare, and their recognition relies on a high level of clinical suspicion supplemented by adequate diagnostic facilities to attain diagnosis. Treatment with immunoglobulin augmentation, haemopoietic stem cell transplantation or gene therapy may ameliorate further end-organ damage, making early diagnosis crucial. Broadly classified into four groups (table 1), primary immunodeficiencies can

Key points

- Common causes of acquired immunodeficiency are immunosuppressive medication (corticosteroids, cytotoxic chemotherapy and biologicals), radiation, HIV infection and asplenia.
- The pathogen type depends on the nature of the underlying immune defects.
- Correct assessment of individual risk factors for pneumonia (community *versus* hospital acquired and immunosuppressed patient) helps to improve treatment.
- Diagnostic and treatment algorithms may help to reduce mortality and the use of antibiotics.
- These algorithms are solely defined for community- and hospital-acquired pneumonia in major guidelines.

Table 1. Classification of primary immunodeficiencies into four broad groups

	Incidence	Mode	Gene	Implication
B-cell deficiency				
Agammaglobulinaemia	1 in 200000	XLR	BTK Xq21.3-q22	*Haemophilus influenzae* (commonest)
		AR	IGLL1 (22q11.21)	*Staphylococcus* *Streptococcus*
			IGHM (14q32.33)	*Pseudomonas* (rare) Enterovirus Poliomyelitis
			LCRR8 (9q34.13)	*Mycoplasma* (arthritis)
CVID	1 in 25000	AD or AR	TNFRSF13B (10%)	Ear, nose, throat and lower respiratory infections Giardia lamblia (GI) Campylobacter (GI)
Hyper IgM syndrome		XLR	HIGM1 (Xq26)	*Pneumocystis jirovecii* *Histoplasma capsulatum* Cryptosporidium: biliary ducts
T-cell deficiency				
Severe combined immunodeficiency (SCID)	1 in 100000	AR or XLR	$T^-B^+NK^-$ $T^-B^-NK^+$ $T^-B^-NK^-$ $T^-B^+NK^+$	Candidiasis Bacterial meningitis Bacterial pneumonia Varicella virus Herpes virus CMV
Ataxia-telangiectasia	1 in 40000	AR	ATM (11q22.3)	Sinusitis Pneumonia
Wiskott–Aldrich syndrome (WAS-related disorders)	3 in 1000000	XLR		*P. jirovecii* Epstein–Barr virus (lymphoma)

(*Continued*)

Table 1. Continued

	Incidence	Mode	Gene	Implication
T-cell deficiency (cont.)				
Hyper IgE syndrome		AR	DOCK8 (9p)	Skin abscesses Gram positive and Gram negative bacterial pneumonia *(H. influenzae)* Fungal pneumonia *P. jirovecii* *H. capsulatum* Herpes viruses (HSV, VZV) Molluscum contagiosum Human papillomavirus
		AD	STAT3	Gram positive pneumonia (pneumatoceles common) *Pseudomonas aeruginosa* *Aspergillus fumigatus* Mucocutaneous candidiasis
Haemophagocytic lymphohistiocytosis (primary forms)	1 in 100000	AR	PFR1 UNC13D STX11 STXBP2	Viral infections: Epstein–Barr virus CMV Parvovirus Herpes viruses *Mycobacterium tuberculosis* *H. capsulatum* *Brucella* Leishmaniasis

(*Continued*)

Table 1. Continued

	Incidence	Mode	Gene	Implication
Phagocytic innate immunodeficiency				
Chronic granulomatous disease (CGD)	1 in 217000	AR	CYBA (16q24) NCF1 (7q11.23) NCF2 (1q25) NCF4 (22q13.1)	Pneumonia, abscesses, cellulitis, adenitis and osteomyelitis *Staphylococcus aureus* *Aspergillus* (invasive frequent) *M. tuberculosis*
		XLR (65%)	CYBB (Xp21.1)	
Leukocyte adhesion deficiency (LAD)	>200 reported	AR	LAD I ITGB2	Bacterial more common than fungal infections Recurrent, severe: skin; mucous membranes: periodontitis and gingivitis Absence of pus at site
	<10 reported	AR	LAD II SLC35C1	Similar features, milder course Muscular flaccidity, mental retardation
	25 reported	AR	LAD III Kindlin3	Infection profile as LAD I Additional bleeding complications
Severe congenital neutropenia (SCN)	1 in 1000000	AD	ELA2 (19p13.3)	Bacterial infections Skin GI Respiratory (upper and lower)
		AR	HAX	Pyogenic bacterial infections Skin Lungs Mouth

(*Continued*)

Table 1. Continued

	Incidence	Mode	Gene	Implication
Complement innate immunodeficiency				
C1q	>40 reported		1p36	SLE-like disease
C3	<30 reported		19p13	Pyogenic infections
C5	>40 reported		9q33–34	Neisserial meningitis
C9	1 in 1000 (Japan)		5p14–p12	Neisserial infections (asymptomatic)
Ficolin 3	<10 reported		1p36	Respiratory infections, necrotising enterocolitis
Factor I	<30 reported		4q25	Severe infections
FHR I (FHR III)	>100 reported		1q32	Infections, atypical haemolytic uremic syndrome (aHUS)
CR3(CD18/CD11b)	1 in 1000000		21q22	LAD

XLR: X-linked recessive; AR: autosomal recessive; AD: autosomal dominant; GI: gastrointestinal; SLE: systemic lupus erythematosus. Reproduced and modified from Grumach *et al.* (2014) with permission.

affect both humoral and cellular immunity, with many clinical manifestations combining both. T-cell mediated immune responses are largely responsible for protecting against yeast, fungi, various viruses and some bacteria. Humoral immune responses are B-cell driven, and protect against other viruses and particularly encapsulated bacteria by secreting antibodies. Although particularly prevalent among newborns, isolated defects in humoral immunity are often compensated over subsequent months by exposure to persisting maternal antibodies in breast milk.

Impaired T-cell or phagocyte function increases the risk of opportunistic infections from particular opportunistic pathogens including *Pseudomonas*, *Burkholderia*, *Pneumocystis jirovecii*, *Aspergillus* and cytomegalovirus (CMV). However, the clinical course varies, late presentation in adults with some syndromes, such as common variable immunodeficiency syndrome (CVID), is not uncommon.

Nontuberculous mycobacterial infections have been described in patients with genetic defects in the interleukin (IL)-12 and interferon (IFN)-γ pathways, as well as in patients with defective regulation of nuclear factor (NF)-κB (NF-κB essential modifier or NEMO defects).

Acquired immunodeficiency

Acquired immunodeficiencies are more prevalent than primary defects and result mainly from the use of cytotoxic chemotherapy and radiotherapy, novel biological treatments, steroid exposure, HIV and solid organ transplantation. In each of these patient groups, there is an increased susceptibility to specific pathogens based primarily on the underlying immunological deficit. In comparison to other treatments, less is known about antibody-based treatments directed towards T- and B-cell function or tumour necrosis factor (TNF)-α, and these should be further evaluated when assessing individual patient risk.

Neutropenia

Infection in neutropenic patients continues to pose major clinical challenges. Host defences are commonly impaired either by the underlying disease in primary deficiencies, or specific treatments or iatrogenic manipulation while hospitalised.

Due to a lack of neutrophil granulocytes, pulmonary infiltrations may be absent or difficult to identify. Current recommendations from the Infectious Diseases Working Party of the German Society of Hematology and Oncology reflect this, recommending urgent thoracic CT in all patients with neutropenic fever failing to respond after 3 days of empirical antibiotic treatment (Maschmeyer *et al.*, 2015). Pulmonary infiltrates, where present, require further investigation through bronchoalveolar lavage (BAL). Storage and transport of BAL samples is of critical importance, with 4°C considered the optimal temperature, and testing should ideally begin within 2–3 h of material recovery. Diagnostic work-up should include mycobacteria (microscopy, culture and PCR), *P. jirovecii* (immunofluorescence and PCR), *Legionella* spp. and galactomannan antigen testing for *Aspergillus*. Viral aetiologies should also be considered, particularly common respiratory pathogens, *via* immunofluorescence or PCR. CMV disease has not been well studied in solid tumour patients. CMV infections (table 2), including CMV pneumonia, may be detected *via* CMV antigen in blood, *i.e.* pp65, or CMV DNA.

The presence of *Candida* spp. only very rarely reflects *Candida* pneumonia, and this is also the case in severely immunocompromised patients. The presence of *Aspergillus* should be taken very seriously and be evaluated as a true pathogen. In the absence of a confirmatory biopsy, diagnostic criteria including specific risk factors, CT criteria and corresponding microbiological findings (positive galactomannan antigen test, culture and PCR) are crucial in assisting with decision-making. All cases of ‘probable’ or ‘proven’ pulmonary aspergillosis should be immediately treated (table 3).

Bone marrow transplantation

Patients undergoing allogenic stem-cell or bone marrow transplantation (BMT) are at understandably high risk of neutropenia, and impairment of barrier defences and both cell-mediated and humoral immunity. The degree of neutropenia reflects both the nature and duration of exposure to the precipitating factor. The resulting deficit facilitates even microorganisms with limited pathogenicity in causing serious infections. Patients undergoing allogenic stem-cell transplantation or BMT are subjected to sequential suppression of host defences, predisposing to variation in susceptibility to particular organisms at different phases following transplantation. The greatest infective risk, particularly of opportunistic pneumonias due to *S. aureus*, *P. aeruginosa*, Enterobacteriaceae, *Aspergillus* spp. or even CMV, occurs within the first few weeks following allogenic stem-cell transplantation.

Solid organ transplantation

Due to their chronic immunocompromised state, infection represents a lifelong threat to patients after solid organ transplantation and remains a leading cause of early and late mortality. In addition to their direct impact, several studies have linked infection

Table 2. Conditions caused by CMV

CMV disease	CMV syndrome
Virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen. It is recommended that both the source of the specimens tested (*e.g.* plasma, serum, whole blood, peripheral blood leukocytes, cerebrospinal fluid, BAL fluid, urine or tissue) and the diagnostic method used should be described clearly.	CMV syndrome is a disease definition only used in solid organ transplant recipients. A 'proven' category cannot be defined. The definition of probable CMV syndrome requires detection of CMV in blood by viral isolation, rapid culture, antigenaemia or NAT together with at least two of the following. 1) Fever ≥38ºC (at least 2 days). 2) New or increased malaise, or new or increased fatigue (toxicity grade 3, Common Terminology Criteria for Adverse Events, National Cancer Institute Version 4.0). 3) Leukopenia or neutropenia on two separate measurements at least 24 hours apart. WBC count of <3500 cells·µL^{-1}, if the WBC count prior to the development of clinical symptoms was ≥4000 cells·µL^{-1}, or a WBC count decrease of >20%, if WBC count prior to the development of clinical symptoms was <4000 cells·µL^{-1}. The corresponding neutrophil counts are <1500 cells·µL^{-1} or a decrease of >20% if the neutrophil count before the onset of symptoms was <1500 cells·µL^{-1}. 4) ≥5% atypical lymphocytes. 5) Thrombocytopenia defined as a platelet count of <100000 cells·µL^{-1} if the platelet count prior to the development of clinical symptoms was ≥115000 cells·µL^{-1} or a decrease of >20% if the platelet count prior to the development of clinical symptoms was <115000 cells·µL^{-1}. 6) Elevation of hepatic aminotransferases (alanine aminotransferase or aspartate aminotransferase) to two times the upper limit of normal (applicable to non-liver transplant recipients).

NAT: nucleic acid test; WBC: white blood cell. Information from Ljungman *et al.* (2017).

response processes with an increased predisposition to allograft rejection, especially in lung transplantation (LTx) (Fuehner *et al.*, 2012).

While classical symptoms such as fever and cough may be masked in solid organ transplant recipients, this problem is of particular concern in LTx patients. In the early post-transplant phase, such infections are most commonly bacterial, followed by fungi and then viruses. *P. aeruginosa* is the predominant pathogen, followed closely by *S. aureus*. Common Gram-negative organisms causing post-transplant pneumonias include *Klebsiella* and *H. influenzae*.

CMV represents the commonest viral pathogen, occurring in approximately one-third of patients during the first year. CMV-naïve recipients (R^{-}) receiving organs from

Table 3. Evidence of Aspergillus *infection*

Serological testing	Direct evidence
PCR or galactomannan on respiratory fluids (no sputum)	Biopsy with fungal hyphae
Serum galactomannan (good in acute invasive disease)	Growth of *Aspergillus* from a cavity
	Sputum potentially contaminated, low sensitivity of sputum culture with standard methods
	Sampling
	BAL/biopsy (both invasive)

Information from Patterson *et al*. (2016).

seropositive donors (D$^+$) are at the greatest risk of infection and are predisposed to particularly severe infection. Current guidelines recommend the use of ganciclovir/valganciclovir prophylaxis in D$^+$/R$^-$ for ≥6 months following transplant (Kotton *et al.*, 2018). A primary CMV infection is defined as the first detection of CMV infection in an individual who has no evidence of CMV exposure before transplantation. Some severely immunocompromised individuals might not develop CMV-specific antibodies. A reinfection means detection of a CMV strain that is distinct from the strain that caused the initial infection, and CMV reactivation is when two viral strains (prior and current) are found to be indistinguishable (either by sequencing specific regions or by molecular techniques). Patients with non-severe infection should receive treatment doses of valganciclovir (900 mg orally twice daily, with dose adjustment for renal insufficiency) or *i.v.* ganciclovir (5 mg·kg^{-1} *i.v.* every 12 h, with dose adjustment for renal insufficiency) until resolution of clinical symptoms, resolution of viraemia, and for a minimum of 2 weeks. Genotypic resistance testing should be performed in patients with suspected ganciclovir resistance. Data on the treatment of ganciclovir-resistant CMV infection are limited. Foscarnet, cidofovir, cytomegalovirus immune globulin or letermovir might be alternative antiviral regiments (Kotton *et al.*, 2018).

Community-acquired respiratory viruses consisting mainly of adenovirus and influenza virus along with certain Paramyxoviridae – respiratory syncytial virus (RSV), parainfluenza virus and human metapneumovirus (hMPV) – have gained recognition as pathogens among LTx recipients. While treatment options remain limited, oral ribavirin may improve outcomes in paramyxoviral infections but may not be well tolerated in all patients (Fuehner *et al.*, 2011).

Fungal infections remain a constant, albeit less common, threat and are usually caused by *Aspergillus* or *Candida* species. However, pulmonary candidiasis is rare, particularly among LTx recipients, and detection should be based on culture and histology of bronchial mucosa biopsies rather than BAL findings. Conversely, the presence of *Candida* in blood cultures should be considered significant, with immediate initiation of treatment. BAL analysis may be negative in up to 40% of patients with an invasive aspergillosis. Infections tend to be limited to the airways, with a preponderance towards bronchial anastomoses. Invasive disease at the anastomoses may result in erosion of the pulmonary artery precipitating catastrophic pulmonary haemorrhage. Voriconazole is the first-line treatment for invasive aspergillosis, with echinocandins and parenteral lipid formulations of amphotericin B used as second-line therapy. *Candida* infections generally respond well to fluconazole. In species other than *Candida albicans*, however, fluconazole resistance is becoming increasingly prevalent.

Due to a combination of lifelong co-trimoxazole prophylaxis and low-dose steroid treatment regimes, *P. jirovecii* pneumonia has become rare among adherent patients.

New immunosuppressive drugs

In recent years, multiple monoclonal antibodies have been licensed for treatment of a wide variety of conditions. Inevitably, subsequent studies have alluded to an increased risk of severe infections in patients receiving antibody-associated immunosuppression. Due to wide variations in immunological interactions, significant variability exists both in the pathogen spectrum and the severity of their effects. Their modes of action can be broadly classified into those affecting B-cell function such as rituximab (anti-CD20), those specifically binding T-cells such as alemtuzumab (anti-CD52), co-stimulatory T-cell antibodies such as abatacept, anti-TNF antibodies such as infliximab, adalimumab and certolizumab, and etanercept (anti-soluble TNF receptor) and tocilizumab (anti-IL-6).

HIV infection

Reduced CD4+ cell counts, while not correlating directly, do appear to indicate an increased risk of opportunistic respiratory pathogens in HIV-infected patients (figure 1). The common bacterial pathogens are *Streptococcus pneumoniae* and *Haemophilus* spp. Intravenous drug use and smoking appear to increase the pneumonia risk in these patients. Worldwide, *M. tuberculosis* is the most important co-infection in HIV-infected patients and significantly influences AIDS-related mortality. *P. jirovecii* is the most common nonbacterial pathogen. *Nocardia* spp., *Actinomyces* spp., *Rhodococcus* and *Cryptococcus* are rare opportunistic pulmonary pathogens occasionally diagnosed in European patients with poorly treated HIV.

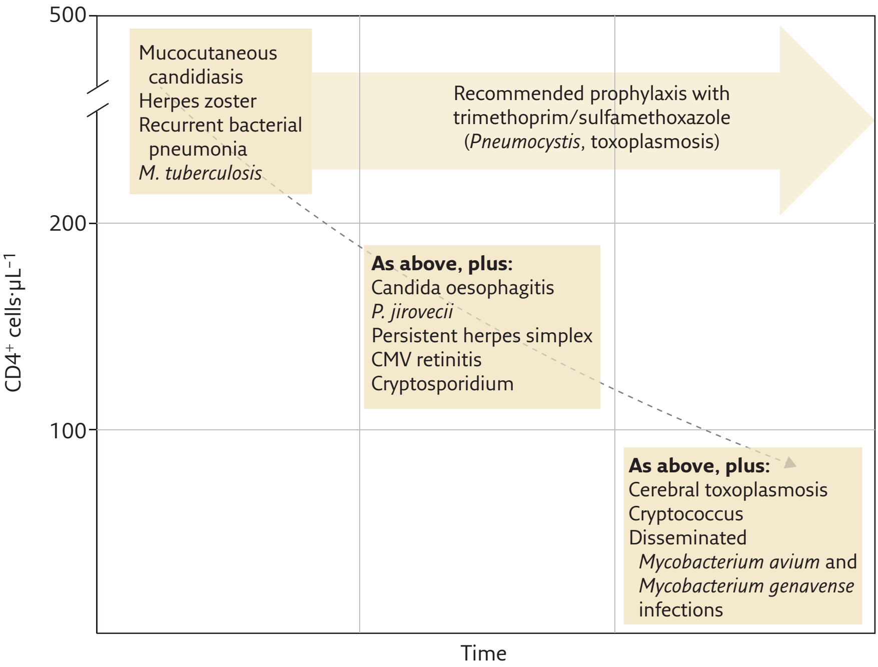


Figure 1. Opportunistic respiratory pathogens in HIV-infected patients.

Asplenia

Antibody production and phagocytosis by splenic macrophages represent a fundamental aspect of defence against encapsulated bacteria. Following splenectomy, patients are at higher risk of infection with *S. pneumoniae*, *Haemophilus* spp. and *Neisseria meningitidis*. Mortality rates from overwhelming post-splenectomy infection (OPSI) are reported to be up to 600 times greater than in the general population. The overall incidence of septicaemia remains low, with an estimated lifetime risk for OPSI of ~5% (Lynch *et al.*, 1996).

Further reading

- Ascioglu S, *et al.* (2002). Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis*; 34: 7–14.
- Benito N, *et al.* (2012). Pulmonary infections in HIV-infected patients: an update in the 21st century. *Eur Respir J*; 39: 730–745.
- Blyth CC, *et al.* (2014). Consensus guidelines for the treatment of invasive mould infections in haematological malignancy and haemopoietic stem cell transplantation, 2014. *Intern Med J*; 44: 1333–1349.
- Curtis JR, *et al.* (2011). The comparative risk of serious infections among rheumatoid arthritis patients starting or switching biological agents. *Ann Rheum Dis*; 70: 1401–1406.
- Fuehner T, *et al.* (2011). Single-centre experience with oral ribavirin in lung transplant recipients with paramyxovirus infections. *Antivir Ther*; 16: 733–740.
- Fuehner T, *et al.* (2012). The lung transplant patient in the ICU. *Curr Opin Crit Care*; 18: 472–478.
- Gottlieb J, *et al.* (2009). Community-acquired respiratory viral infections in lung transplant recipients: a single season cohort study. *Transplantation*; 87: 1530–1537.
- Grumach AS, *et al.* (2014). Are complement deficiencies really rare? Overview on prevalence, clinical importance and modern diagnostic approach. *Mol Immunol*; 61: 110–117.
- Hodinka RL (2003). Human cytomegalovirus. *In:* Murray BE, ed. Manual of Clinical Microbiology. 8th Edn. Washington, ASM Press; pp. 1304–1318.
- Keyser FD (2011). Choice of biologic therapy for patients with rheumatoid arthritis: the infection perspective. *Curr Rheumatol Rev*; 7: 77–87.
- Kotloff RM, *et al.* (2011). Lung transplantation. *Am J Respir Crit Care Med*; 184: 159–171.
- Kotton CN, *et al.* (2018). The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation*; 102: 900–931.
- Kumar D, *et al.* (2010). A prospective molecular surveillance study evaluating the clinical impact of community-acquired respiratory viruses in lung transplant recipients. *Transplantation*; 89: 1028–1033.
- Ljungman P, *et al.* (2017). Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. *Clin Infect Dis*; 64: 87–91.
- Lynch AM, *et al.* (1996). Overwhelming postsplenectomy infection. *Infect Dis Clin North Am*; 10: 693–707.
- Maschmeyer G, *et al.* (2015). Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients (allogeneic SCT excluded): updated guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Oncol*; 26: 21–33.

- Meersseman W, *et al.* (2009). Significance of the isolation of *Candida* species from airway samples in critically ill patients: a prospective, autopsy study. *Intensive Care Med*; 35: 1526–1531.
- Palmer SM, *et al.* (2010). Extended valganciclovir prophylaxis to prevent cytomegalovirus after lung transplantation: a randomized, controlled trial. *Ann Intern Med*; 152: 761–769.
- Patterson TF, *et al.* (2016). Executive summary: practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*; 63: 433–442.
- Schaberg T, *et al.* (2010). Management der Influenza A/H1N1 – Pandemie im Krankenhaus: Update Januar 2010. Eine Stellungnahme der Deutschen Gesellschaft fur Pneumologie und Beatmungsmedizin [Management of a new influenza A/H1N1 virus pandemic within the hospital. Statement of the German Society of Pneumology]. *Pneumologie*; 64: 124–129.
- Strassburg A, *et al.* (2010). Infektionsdiagnostik in der Pneumologie [Diagnosis of infections in pneumology]. *Pneumologie*; 64: 474–487.

Aspiration pneumonitis

John MacSharry and Desmond M. Murphy

The term aspiration refers to the passage of foreign material into the lungs. Gastro-oesophageal reflux (GOR) refers to reflux of stomach contents into the oesophagus, which may or may not lead to subsequent aspiration of these contents into the oropharynx and thereafter into the airway. Therefore, while these two events may be linked, they are not necessarily the same.

Aspiration of gastric fluids may cause damage to airway epithelium, not only because the acidity of the aspirate may have a toxic irritant effect on bronchial epithelial cells but also due to the potential actions of digestive enzymes such as pepsin and bile salts on these cells. Research has shown that direct instillation of these factors to airway epithelia causes damage with an inflammatory response.

The clinical syndrome resulting from such aspiration will depend on factors such as the quantity, frequency and nature of the aspirate, as well as an individual's host response. In healthy subjects, small amounts of aspirated material can be cleared by host defence mechanisms without consequence. However, in patients with impaired immunity or clearance mechanisms the impact may have clinical consequences of varying severity. In addition, patients with impaired swallowing mechanisms, *e.g.* resulting from neurological conditions, alcohol, decreased levels of consciousness or intubation, are predisposed to aspiration and its implications.

Aspiration of large amounts of gastric acid will result in the induction of a chemical injury to the airways and lung parenchyma. The initial insult triggers a cascade of inflammatory responses with the recruitment of inflammatory cells and the release of various inflammatory mediators. Large volume gastric acid aspiration may cause an acute lung injury, with diffuse alveolar damage and pneumonitis. This syndrome is often referred to as Mendelson's syndrome. By contrast, recurrent, small volume, microaspiration during sleep may occur without consequence or result in chronic and less severe forms of lung injury. In individuals who aspirate, recurrent respiratory tract infections are a common consequence, with the ensuing development of bronchiectasis a possible end-stage manifestation. Furthermore, experimental

Key points

- Aspiration may cause a wide spectrum of pulmonary complications.
- Aspiration is also common in lung disease.
- Aspiration may induce airway injury and infection.
- Evidence supporting the targeting of aspiration is lacking.

models suggest that the normal host inflammatory response to infection exhibited by macrophages may be inhibited due to weakly acidic conditions.

Infectious aspiration results in an increased number of microbes in the lung and may lead to aspiration pneumonia. The microbial species introduced into the lung are mixed and vary depending on site and patient situation. Chemical pneumonitis can also progress to infectious pneumonia due to the inflammatory insult and resulting reaction to the resident lung microbiota. While the predominant cause of pneumonia in adults is the Gram-positive *Streptococcus pneumoniae*, a normal upper respiratory tract resident, aspiration pneumonia is generally caused by resident bacterial microbiota from other body sites, in particular the mouth and gut. These species can be both aerobic and anaerobic; bronchial sampling of aspiration pneumonia in elderly patients revealed aerobic bacteria such as the Gram-positive cocci (*Streptococcus* spp., *S. pneumoniae* and *Staphylococcus aureus*) and the Gram-negative bacilli (*Haemophilus influenzae, Escherichia coli, Klebsiella pneumoniae, Serratia* spp., *Proteus mirabilis, Enterobacter cloacae* and *Pseudomonas aeruginosa*). Anaerobic bacteria, such as *Prevotella* spp., *Fusobacterium* spp., *Bacteroides* spp., *Porphyromonas gingivalis* and *Peptostreptococcus* spp., can also be found. Indeed, the Gram-negative enteric bacteria (*H. influenzae, E. coli* and *K. pneumoniae)* were the most common species found in aspiration pneumonia followed by the Gram-positive *S. aureus*. Many of these are ESKAPE microbes. ESKAPE is an acronym for the following bacteria (both Gram-positive and negative species): *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. The ESKAPE microbes cause over 60% of all hospital infections and are a clinical concern due to their ability to avoid antibacterial therapy, by resistance methods such as beta-lactamase and biofilm formation.

Large volume, acute aspiration may therefore cause a chemical pneumonitis, a chemical pneumonitis with subsequent secondary infection or an infective aspiration pneumonia. Whether or not antibiotics should be used to prevent secondary infection remains controversial. Where infection is present, antibiotic regimens generally utilise antibiotics to cover a wide variety of aerobic and anaerobic organisms, and include co-amoxiclav (often in combination with metronidazole), piperacillin-tazobactam, clindamycin or carbapenems. The choice of which agent to use is generally dictated by the severity of the infection and local guidelines. Low volume, chronic aspiration is often more difficult to detect and may result in chronic respiratory infection and/or several other respiratory conditions as outlined in the following sections. While not synonymous with GOR, chronic aspiration often occurs in tandem with GOR.

Detecting aspiration

The clinical presentation of aspiration syndromes is dependent on multiple factors including the extent and duration of the aspiration (in terms of volume and chronicity), the contents of the aspirate and the host response.

The typical symptoms of GOR include heartburn and epigastric discomfort. Extra-oesophageal symptoms may include hoarseness, cough or wheeze. These symptoms may be related to meals or patient position. However, GOR may occur without symptoms, so-called ‘silent reflux’, with possible ‘silent aspiration’. This should be suspected in individuals presenting with recurrent respiratory tract infections. Objective testing methods include ambulatory 24-h oesophageal pH monitoring with intraluminal impedance testing, which is widely accepted as the current ‘gold standard’ for diagnosing gastro-oesophageal reflux disease (GORD). Combining pH monitoring and impedance allows detection of both acid and non-acid reflux, which would be potentially missed using pH testing alone. Other tests that have been used include Barium swallow with provocation. While Barium swallow has a detection rate for GOR as low as 50%, with the addition of provocation manoeuvres this can be greatly improved, and the test is relatively inexpensive and noninvasive.

Although dual chamber pH and impedance monitoring both detect proximal reflux, they do not offer a quantitative assessment of the extent of reflux or a measurement of airway aspiration. The measurement of pepsin and bile salts in airway secretions have been proposed as surrogate markers of aspiration of gastric and duodenal contents into the lung.

Possible therapeutic approaches

Therapeutic strategies aimed at reducing GOR and aspiration include:

- lifestyle modification (weight loss, avoidance of food triggers, stress reduction and altered patient positioning),
- pharmacological approaches (antacids, histamine antagonists, proton pump inhibitors and the use of prokinetic agents),
- endoscopic treatment, and
- anti-reflux surgeries.

However, in general studies examining the impact of these strategies on pulmonary related outcomes are either lacking or have produced mixed results. In aspiration pneumonia, antibiotic therapy is indicated as outlined earlier.

Specific pulmonary conditions

Acute lung injury or acute respiratory distress syndrome

Aspiration-induced lung injury is postulated to account for a significant proportion of acute pulmonary dysfunction in critically ill patients and often goes unrecognised in this group. Despite this, aspiration is well recognised as an independent risk factor for the subsequent development of pneumonia or acute lung injury or acute respiratory distress syndrome (ALI/ARDS).

Post-transplant obliterative bronchiolitis

Non-alloimmune injuries have been increasingly recognised as risk factors for obliterative bronchiolitis (OB) post-lung transplantation, the major barrier to long-term allograft success and patient survival. GOR with associated chronic aspiration appears to represent a significant injury to lung allografts, with up to 75% of patients having demonstrable GORD with impedance or biomarker presence following lung transplantation. Reflux episodes on pre-transplant impedance and pH testing have also been associated with a decreased time to early allograft injury after lung transplantation. Anti-reflux surgery may be associated with increased survival and improved lung function. In particular, fundoplication performed early post-transplant may result in a significant reduction in the incidence of obliterative bronchiolitis.

Bronchiectasis

The reported prevalence of GORD in bronchiectasis ranges from 11% to 75%, with observational studies suggesting that GORD is associated with increased clinical severity, increased bacterial colonisation rates and reduced quality of life in bronchiectasis patients. Further studies have suggested a relationship between the presence of GORD in this population and nontuberculous mycobacteria. However, data supporting targeting of GOR and aspiration remains limited.

Cystic fibrosis

Patients with CF are predisposed to reflux as a result of delayed gastric emptying and dysmotility. The European Epidemiologic Registry of Cystic Fibrosis reported that patients with both CF and GORD had impaired lung function compared with those without GORD. Studies have also reported a potential relationship between reflux and colonisation with *P. aeruginosa*. In children with CF, elevated bronchoalveolar lavage (BAL) fluid pepsin has been associated with high interleukin (IL)-8 levels. In addition, concentration of bile acids has been shown to correlate with neutrophil elastase in sputum, degree of lung function impairment, and the need for antibiotic treatment. Retrospective reviews and case series have suggested a possible benefit for fundoplication in terms of reductions in exacerbation rates and improvements in lung function.

COPD

In COPD, numerous studies have suggested a relationship between exacerbations and GOR, although a relationship between GOR and an effect on lung function is less clear. In a Japanese study, treatment of COPD patients with a proton-pump inhibitor (PPI) demonstrated a reduction in exacerbation rate. Whether or not this was secondary to neutralisation of acidic aspirate is unclear.

Pulmonary fibrosis

There is a high prevalence of GOR in idiopathic pulmonary fibrosis (IPF). Increased pepsin in BAL fluid has been associated with exacerbations and a more aggressive disease phenotype, suggesting a possible association with aspiration. Studies have reported that aggressive targeting of reflux resulted in improved clinical outcomes.

Asthma

GORD has a high prevalence in asthma with reported rates of 25–80%. However, although GORD and asthma are frequently seen as comorbid conditions, a definite causal relationship is difficult to establish.

A significant association between the presence of GORD and an increased frequency of exacerbations and hospitalisations in asthmatic patients has been noted.

Numerous studies and, more importantly, clinical trials examining the potential of PPIs to improve airways disease in asthma have demonstrated mixed findings. Small case series and retrospective reviews of patients with GOR and asthma have suggested benefit in terms of exacerbation and lung function. However, we recently reported a study of 78 asthma patients of varying severity stratified according to Global Initiative for Asthma (GINA) guidelines and showed detectable BAL pepsin in 59% patients. However, no significant associations between pepsin level and disease severity, measures of asthma control, lung function, quality of life or exacerbation frequency were noted, suggesting that the importance of aspiration on asthma outcomes may be overstated.

Conclusion

Aspiration represents an injurious insult to the airway, the severity and outcome of which depends on multiple factors. There is a wide spectrum of severity of the potential insult to the airway ranging from overt aspiration to GOR and microaspiration. How, when and what severity of aspiration needs to be present before targeting the condition remains unclear, as does the method of targeting.

Further reading

- Hu X, *et al.* (2015). Aspiration-related pulmonary syndromes. *Chest*; 147: 815–823.
- Hunt EB, *et al.* (2018). Gastric aspiration and its role in airway inflammation. *Open Respir Med J*; 12: 83.
- Marik PE (2001). Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med*; 344: 665–671.
- Raghavendran K, *et al.* (2011). Aspiration-induced lung injury. *Crit Care Med*; 39: 818–826.

Pulmonary tuberculosis

Giovanni Sotgiu and Giovanni Battista Migliori

The World Health Organization (WHO) has declared TB a global emergency due to its burden in terms of morbidity and mortality, in comparison with other infectious and noninfectious diseases. The epidemiological scenario has been recently worsened by:

- The high proportion of TB patients co-infected with HIV
- Multidrug resistance to anti-TB drugs (*i.e. Mycobacterium tuberculosis* strains resistant to at least isoniazid and rifampicin)
- Migration from high-incidence countries
- Social determinants of the infection and disease (in particular, poverty, drug abuse, malnutrition and homelessness)

TB can affect virtually every organ (mainly the lungs, *i.e.* pulmonary tuberculosis (PTB); 50–70% of all TB cases) or body system. PTB is the most important clinical form: it mainly affects young adult patients and could be epidemiologically relevant for the transmission of *M. tuberculosis* strains from index cases to susceptible individuals in the community or in congregate settings. Several observational and experimental studies, as well as systematic reviews, have proven the poor effectiveness of the bacille Calmette–Guérin (BCG) vaccine in the prevention of its occurrence.

Aetiology

TB is an infectious disease caused by nonmotile, non-spore-forming bacteria belonging to the family *Mycobacteriaceae* in the order *Actinomycetales*. Among the species belonging to the *M. tuberculosis* complex (*Mycobacterium africanum*,

Key points

- With >10 million new cases and >1 million deaths in 2016, TB is a first-class health priority.
- Diagnosis of pulmonary TB is simple, being primarily based on bacteriology (sputum smear microscopy and culture). New rapid diagnostics (Xpert MTB/RIF and line probe assays) for the rapid diagnosis of TB and drug resistance have been recommended to detect TB early and treat difficult-to-manage patients.
- Treatment of pan-susceptible cases of pulmonary TB is effective and cheap, while treatment of drug-resistant TB is possible but takes longer, and is more difficult and expensive.
- New drugs and regimens are likely to appear in the future.

Mycobacterium bovis, *Mycobacterium canettii*, *Mycobacterium caprae*, *Mycobacterium microti* and *Mycobacterium pinnipedii*), the most important agent of human disease is *M. tuberculosis*. Mycobacteria are 2–4 μm long and 0.2–5 μm wide, and characterised by a bacterial multiplication times of 18–24 h. They can exist both in aerobic and anaerobic environments, hence their ability to survive within the granuloma, macrophage cytoplasm and phagolysosome. They are defined as acid-fast bacilli following Ziehl–Neelsen staining, owing to their cell wall structure, which is rich in mycolic acid, a high molecular weight fatty acid involved in the immunopathogenesis of the infection and in drug resistance mechanisms. However, their immunopathogenesis is based on the involvement of other molecules and several complicated mechanisms (*e.g.* lipoarabinomannan, phenolic glycolipids, secreted proteins and immune evasion). A structure characterised by an elevated concentration of carbohydrates involved in cell–cell interactions represents the outermost section of the *M. tuberculosis* envelope. The peptidoglycan network confers rigidity to the cell wall and protects a genome with ~4000 genes (4.4×10^6 bp). Two groups of genes are crucial to mycobacterial physiology: one encoding β-oxidation related-enzymes aimed at supporting energetic activities; and the other encoding PE/PEE/PGRS families (10% of mycobacterial coding capacity) of proteins potentially associated with mycobacterial virulence and molecular mimicry. Furthermore, another important group of genes are those encoding the synthesis of glycolipids of the envelope, which interact with the innate and adaptive immune system of human beings, as well as with anti-TB drugs.

Pathogenesis

M. tuberculosis strains can be spread through air droplets from infectious PTB individuals while coughing, sneezing or speaking. Close contacts (*i.e.* those with prolonged (>8 h) and/or intense contact with contagious cases) are at highest risk of becoming infected after an infectious exposure. Therefore, airborne transmission directs the infection control interventions and measures (*e.g.* respirators and ultraviolet light in a room) adopted in community and healthcare settings. Climate and human population density may affect the intensity and/or duration of human relationships and, consequently, the probability of exposure and close contact with an infectious index case. *M. tuberculosis* strains included in droplet nuclei sized >5 μm are trapped by the nasal vibrissae and by the mucus of the goblet cells, whereas the cilia of the epithelial cells remove them. Environmental factors (*e.g.* humidity, temperature and ventilation) can affect droplet size and density. Droplet nuclei sized 1–5 μm can reach the alveoli, particularly those located in right lower lobes, where they are engulfed by macrophages, which are part of the innate immune system; their activation does not require a previous antigenic exposure. *M. tuberculosis* strains are then transferred to draining lymph nodes and prime naïve lymphocytes, including T- and B-cells. The significant multiplication rate during the first 3 weeks is downregulated by phagocytic cells, functionally activated mainly by T-cells producing interferon (IFN)-γ, which is, quantitatively, the most represented cytokine. It is estimated that a long-lasting infection could be favoured by the slow enrolment of T-cells ($CD4^+$ and/or $CD8^+$ T-cells). Numerous bacterial and host mechanisms are involved in the pathogenesis of the infection:

- mycobacterial mannose-capped lipoarabinomannan, lipomannan, arabinomannan, mannan and mannoglycoproteins
- ligands for macrophage mannose receptors
- Toll-like receptors and cytokines (interleukin (IL)-12, tumour necrosis factor, *etc.*)
- IL-15 (proliferation of natural killer cells and apoptosis prevention)

- T-cells (cytotoxic T-cells, helper T (Th)1-cells, Th17-cells and regulatory T-cells) and B-cells
- Platelets

In numerous cases, innate and adaptive immunity cannot eradicate mycobacterial strains and a latent TB infection (LTBI) follows; few cases of infection can directly progress to pulmonary disease (the primary progressive form, the incidence of which can be higher in children aged ≤4 years and immunocompromised patients). During the initial phase of the infection (2–12 weeks), *M. tuberculosis* multiplicates slowly (*i.e.* a cell division every 25–35 h) and T-cells are attracted by cytokines released by macrophages. However, in the following phase, granulomata (sized from 1 mm to 2 cm) around mycobacteria arise with the aim of limiting bacterial multiplication and spread to other anatomical sites and, then, establishing latency of the infection. Granulomata are characterised by several macrophage populations secreting pro- and anti-inflammatory cytokines, and by a chemophysical microenvironment inducing *M. tuberculosis* dormancy genes. $CD4^+$ T-cells, primed in the regional lymph nodes and migrating to the primary site of infection, produce cytokines that enrol $CD8^+$ lymphocytes (*e.g.* IL-15), activate regulatory T-cells and inhibit mycobacterial multiplication (*e.g.* IFN-γ). Fibrosis and calcification usually develop in immunocompetent hosts, whereas primary progressive PTB can occur in immunocompromised patients.

Infected individuals developing PTB usually experience the disease within the first 2 years following infection. Dormant bacilli, however, may persist before being reactivated following a temporary or permanent immune depression. It is estimated that the lifetime risk of developing TB is 5–15% in immunocompetent individuals with LTBI; however, impaired immunity significantly increases the risk (*e.g.* annual risk in HIV-positive patients is 5–10%). Age is an important determinant of the risk of disease. The incidence is highest in children and toddlers (35–50% in close contacts of contagious patients), with a second peak during adolescence and early adulthood. The risk may increase in the elderly because of age-related immunity impairment and co- or multimorbidity (*e.g.* diabetes mellitus, chronic renal failure, silicosis, gastrectomy, jejunoileal bypass, solid tumours, haematological malignancies or auto-immune diseases treated with anti-TNF-α drugs).

Epidemiology

WHO estimates that 10.4 (range 8.8–12.2) million new cases of TB occurred in 2016. >60% of the estimated cases were adults (90%) and male (65%). India, China, the Philippines, Indonesia and Pakistan recorded the highest incidence. The WHO South-East Asia region (45%), WHO African region (25%) and WHO Western Pacific region (17%) account for the majority of the cases. TB/HIV co-infection was detected in 10% (range 8%–12%) of the estimated TB cases in 2016. The estimated incidence in the WHO European Region was 290000 (range 251000–333000) in 2016.

It was estimated that 540000–660000 (best estimate 600000 individuals) cases of multidrug-resistant (MDR)/rifampicin-resistant (RR)-TB emerged worldwide in 2016. Most of the cases were estimated in China, India and the Russian Federation. A total of 30 countries recorded the highest MDR-TB incidence: nine countries were in the WHO European Region. The proportion of MDR/RR-TB cases in new and previously treated TB cases is 4.1% and 19% globally, respectively; however, those percentages are significantly higher in the WHO European Region (19% and 55%, respectively). The estimated mortality rate in MDR/RR-TB patients was 240000 (range 140000–340000). In 2006, a new drug-resistant form of TB was described and defined as extensively drug-resistant (XDR)-TB, which is caused by MDR *M. tuberculosis* strains resistant to any fluoroquinolones and to at least one of the second-line injectable drugs (amikacin, capreomycin and kanamycin). At least one case of XDR-TB was notified by 123 WHO member states; the proportion of XDR-TB patients was 6.2% in a cohort of MDR-TB cases. Globally, drug susceptibility testing (DST) to diagnose MDR/XDR-TB is performed only for few cases due to the poor laboratory capacity in some settings, leading to the prescription of biased therapeutic regimens and then poor treatment outcomes. Moreover, programmatic shortcomings in the diagnosis and treatment of drug-resistant cases can favour the emergence and spread of further drug resistances.

~1.3 (range 1.2–1.4) million HIV-negative TB patients died in 2016, whereas an estimated 374000 (range 325000–427000) HIV-positive patients died. Annual mortality rate is falling at ~3%, whereas annual incidence is falling at ~2%. From 1990 to 1997, TB incidence decreased but the positive trend was reverted by the HIV/AIDS epidemic and by the occurrence of drug-resistant cases; however, the implementation and scale-up of several preventive measures, as well as the distribution of successful antiretroviral drugs, has favoured a positive declining trend since 2004. The current epidemiological annual decline is too low to achieve TB elimination by 2050.

Clinical features

Before the HIV/AIDS epidemic, almost two-thirds of all TB cases were pulmonary; an increase in extrapulmonary tuberculosis (EPTB), and pulmonary and extrapulmonary forms has been reported, particularly in immunocompromised patients.

Primary PTB frequently occurs without clinical signs and symptoms or can show mild symptoms resembling a lower respiratory tract infection.

In the majority of cases, the infection is contained by innate and adaptive immunity. Mostly in children, recent contacts and individuals with impaired immunity (*e.g.* HIV/AIDS, chronic exposure to anti-TNF-α, haemodialysis, solid organ or haematological transplant recipients and the undernourished), the infection can progress to pleural effusion or induce fever, cough, pain and dyspnoea. In children aged <4 years, a systemic form and/or TB meningoencephalitis can occur after a regional lymphadenitis.

Secondary PTB results from mycobacterial reactivation of a LTBI, and is frequently located where the oxygen concentration is higher (upper lobes) and *M. tuberculosis* multiplication is favoured.

The most frequently detected clinical signs and symptoms are: low-grade fever, asthenia, weight loss (caused by loss of appetite and altered metabolism associated with systemic inflammatory response to mycobacteria), night sweats, mucopurulent cough lasting ≥2–3 weeks. Haemoptysis (*i.e.* coughing up of blood, from a few drops to >500 mL in 24 h) might be due to the rupture of a vessel in a cavity (Rasmussen's aneurysm) or to an aspergilloma in an old cavity, and usually occurs in the late stages of the disease. A pleuritic process can be associated with chest pain.

Diagnosis

Sputum smear microscopy (Ziehl–Neelsen staining) is the most widely used technique for the diagnosis of PTB. Although highly specific, the lower limit of detection of microscopy is $0.5–1 \times 10^4$ organisms per mL sputum and only about half of all culture-positive cases have sputum smear-positive results. At least two or three sputum samples should be sent to the laboratory, with at least one collected early in the morning. Sensitivity may be lower in HIV-positive individuals and children, in whom the bacillary load is poor. Microscopy is simple to perform but suboptimal results can be achieved when adequate internal and external quality assurance programmes are absent. Fluorescence microscopy can add 10% sensitivity to that of conventional light microscopy. An increased sensitivity of 10–20% can be obtained after centrifugation and/or sedimentation. WHO has proposed a case definition for sputum smear-negative PTB based on three negative sputum smears, radiographic abnormalities consistent with active PTB and no response to a course of broad-spectrum antibiotics.

Sputum induction with hypertonic saline is a useful technique in individuals who are either sputum smear negative or unable to produce sputum. Repeated sputum induction increases the yield of both smear microscopy and culture. This diagnostic procedure should be carefully carried out in a well-ventilated setting, being at highest risk of mycobacterial exposure for healthcare personnel.

TB patients can be early detected with molecular techniques. WHO has endorsed a molecular technique (Xpert MTB/RIF; Cepheid, Sunnyvale, CA, USA) for the rapid (~1 h 45 min) diagnosis of TB and rifampicin resistance, which is deemed a surrogate marker of MDR-TB. In 2012 and 2018, this technique was strongly recommended by the European Union standards for TB care.

Mycobacterial solid and liquid cultures are considered the diagnostic gold standard by WHO; however, false-positive results can occur following laboratory contamination. Several weeks are required for a definitive result, although liquid media has decreased time gaps. DST for first- and second-line drugs can help assess the phenotype of the isolated strain.

Molecular techniques (NAATs) can be useful for a rapid diagnosis. Line probe assay technology, based on PCR and reverse hybridisation methods, can be used to detect *M. tuberculosis*-positive samples and mutations associated with antibiotic resistance (*e.g.* resistance to fluoroquinolones and second-line injectables). Whole-genome sequencing represents the technology of the future: genotyping the entire mycobacterial DNA can help in the management of an outbreak and in the identification of DNA sequences linked to antibiotic resistance.

Chest radiology (figure 1) and CT can complement bacteriological examinations, although over- and under-reading have been described. Chest radiography is useful for screening risk groups and is recommended to rule out active TB when diagnosing LTBI.

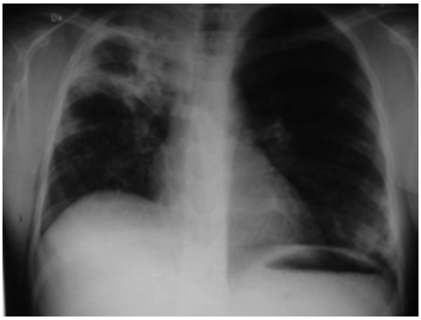


Figure 1. Improvement of PTB with a large cavity in the right upper lobe following adequate treatment.

Among the tools available to detect mycobacterial infection, the TST is widely adopted to assess the immune response against mycobacterial antigens, even if several limitations, including poor specificity, difficult administration and the risk of anergy are reported. It can detect adaptive delayed immunity after the intradermal injection of a protein precipitate (purified protein derivative (PPD)) in the volar part of the forearm (Mantoux test). PPD, which is a combination of different molecules, is derived by filtration of *M. tuberculosis* cultures.

False-negative reactions can occur in immunocompromised patients and in those with PTB. Positive reactions can be found when patients are infected with *M. tuberculosis* (*e.g.* LTBI) or by nontuberculous mycobacteria (NTM), or when immunised with *M. bovis* BCG vaccine (PPD cross-reactivity).

IGRAs can detect adaptive cellular immune reactivity towards *M. tuberculosis*-specific antigens encoded by genes located in the RD-1 genomic region. Promising results on their application for the diagnosis of the disease using biological material from the site of the infection should be confirmed. These techniques can increase the low specificity of TST based on the immune response (release of IFN-γ) to the 6-kDa early secreted antigenic target protein (ESAT-6), the 10-kDa culture filtrate protein (CFP-10) and TB7.7, which are not produced by *M. bovis* BCG or the majority of NTM. Both TST and IGRAs are recommended by WHO for the diagnosis of LTBI in individuals without PTB and/or EPTB when they show high risk of developing disease (children, HIV-positive patients, those exposed to anti-TNF-α, those undergoing dialysis, silicosis patients, contacts of pulmonary cases and patients who will undergo haematological or solid organ transplantation).

Treatment

Sputum smear- and culture-positive TB patients are the main source of *M. tuberculosis* transmission in the community owing to their high bacillary load. The most relevant priority in national and local TB control programmes is the rapid detection of new cases of sputum smear-positive PTB and their effective treatment. Therapeutic regimens for drug-susceptible TB are divided into an initial or bactericidal phase and a continuation or sterilising phase.

WHO recommends treatment of new cases of PTB with a standardised regimen of four first-line anti-TB drugs, including isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months (intensive phase), followed by isoniazid and rifampicin for 4 months (continuation phase) (tables 1–3).

Individuals with a previous TB diagnosis and treated with anti-TB drugs are at higher risk of being infected with drug-resistant strains and, consequently, DST is key. In settings where rapid molecular DST is available, the results should guide the choice of the treatment regimen.

In settings where the prevalence of MDR-TB is high, cases should be managed as if they harbour MDR-TB strains. While rapid molecular methods allow a first orientation, DST for all second-line drugs should be promptly requested to allow the design of an adequate regimen. The appropriate regimen should be chosen in case of monoresistance to isoniazid or rifampicin. In geographical settings where the prevalence of isoniazid monoresistant *M. tuberculosis* strains is high, conventional DST should be always performed, the probability of a false-negative result with Xpert MTB/RIF being high.

Treatment duration is identical in HIV-positive and -negative patients. Antiretroviral therapy should be started immediately after the prescription of the anti-TB therapy,

Table 1. Drugs prescribed for drug-susceptible TB: dosages and common adverse effects

Anti-TB drug	**Recommended daily dosage**	**Common adverse effects (not exclusive)**
Isoniazid	5 $mg \cdot kg^{-1}$ once daily Should not exceed 300 mg per day (10–15 $mg \cdot kg^{-1}$ in children) Always consider co-administration of vitamin B6	Elevated transaminases Hepatitis Peripheral neuropathy GI intolerance CNS toxicity
Rifampicin	10 $mg \cdot kg^{-1}$ once daily (10–20 $mg \cdot kg^{-1}$ in children)	Elevation of liver enzymes Hepatitis Hypersensitivity Fever GI disorders: anorexia, nausea, vomiting, abdominal pain Discolouration (orange or brown) of urine, tears and other body fluids Thrombocytopenia
Ethambutol	800–1600 $mg \cdot day^{-1}$ for those weighing 40–90 kg	Optic neuritis Hyperuricaemia Peripheral neuropathy (rare)
Pyrazinamide	1000–2000 $mg \cdot day^{-1}$ for those weighing 40–90 kg	Arthralgia Hyperuricaemia Toxic hepatitis GI discomfort
Group 3: fluoroquinolones		
Levofloxacin	500–1000 mg once daily	GI discomfort CNS disorders Tendon rupture (rare) Hypersensitivity *Clostridium difficule* colitis
Ciprofloxacin	500–750 mg twice daily	GI discomfort CNS disorders Tendon rupture (rare) Hypersensitivity *C. difficule* colitis
Moxifloxacin	400 mg once daily	GI discomfort Headache Dizziness Hallucinations Increased transaminases QT prolongation *C. difficile* colitis

(*Continued*)

Table 1. Continued

Anti-TB drug	Recommended daily dosage	Common adverse effects (not exclusive)
Group 4: second-line oral agents		
Rifabutin	150–450 mg once daily Consider monitoring drug levels	Anaemia GI discomfort Discolouration (orange or brown) of urine and other body fluids Uveitis Elevated liver enzymes
Ethionamide	750–1000 mg once daily	Severe GI intolerance Nausea Vomiting Hepatitis CNS disorders
Prothionamide	750–1000 mg once daily	Severe GI intolerance Nausea Vomiting Hepatitis CNS disorders
Cycloserine	250 mg three times daily Maximum 1000 mg·day^{-1}	CNS disorders Anxiety Confusion Dizziness Psychosis Seizures Headache
Terizidone	250 mg three times daily Maximum 1000 mg·day^{-1}	CNS disorders Anxiety Confusion Dizziness Psychosis Seizures Headache
PAS	4000 mg three times daily	GI intolerance Nausea Diarrhoea Vomiting Hypersensitivity
Thioacetazone	50 mg three times daily	Hypersensitivity GI intolerance Vertigo Hepatitis
Group 5: oral reserve drugs with uncertain anti-TB activity		
Linezolid	600 mg once daily (600 mg twice daily recommended for MRSA and VRE infections)	Thrombopenia Anaemia Neuropathy

(Continued)

Table 1. Continued

Anti-TB drug	**Recommended daily dosage**	**Common adverse effects (not exclusive)**
Clofazimine	100 mg once daily	Ichthiosis GI discomfort Nausea Vomiting Discolouration of the skin
Amoxicillin–clavulanate	875–125 mg twice daily or 500–250 mg three times daily	GI discomfort Diarrhoea Rash
Clarithromycin	500 mg twice daily	GI discomfort

GI: gastrointestinal; CNS: central nervous system; PAS: para-aminosalicylic acid; MRSA: methicillin-resistant *Staphylococcus aureus*; VRE: vancomycin-resistant *Enterococcus*.

irrespective of $CD4^+$ cell counts, to reduce the risk of death. However, drug–drug interactions, a relevant pill burden and the potential occurrence of immune reconstitution inflammatory syndrome can hinder adequate management.

Rifamycins (mainly rifapentine and rifampicin), which are key drugs in the management of co-infected patients, can induce several enzymes involved in the metabolism of HIV drugs (*e.g.* cytochrome P450 3A). Efflux pumps and drug transporters can be upregulated by rifamycins, decreasing the drug concentration. Protease inhibitors, non-nucleoside reverse transcriptase inhibitors and CCR5 antagonists can show low serum levels when co-administered with rifampicin, increasing the probability of HIV therapeutic failure. An interaction has been described between rifampicin and uridine diphosphate glucuronosyl transferase 1A1, which is involved in the metabolism of integrase inhibitors.

WHO recommends shorter and longer MDR-TB regimens. The duration of the standardised shorter regimen ranges from 9 to 12 months; the drug combination is kanamycin (amycacin), moxifloxacin, prothionamide (ethionamide), clofazimine, pyrazinamide, high-dose isoniazid and ethambutol for the first 4–6 months, and moxifloxacin, clofazimine, pyrazinamide and ethambutol for another 5 months. The probability of treatment success is similar to that recorded in cohorts treated with longer regimens and the default rate is lower; however, treatment failure and relapse rates are higher. However, several epidemiological studies have underscored the high prevalence of drug-resistant *M. tuberculosis* strains in some geographical areas, which decreases the probability of being treated with this standardised regimen.

Longer regimens should be designed including sequential TB drugs according to table 2.

Management of MDR/XDR-TB cases is more complicated from a clinical and public health perspective, the prescribed drugs being more expensive, more toxic and less effective.

Treatment of MDR- and XDR-TB cases should be managed in highly specialised reference centres by skilled healthcare workers identified by national authorities. Relevant clinical decisions (*e.g.* when to start and interrupt treatment, how to design the regimen and how to manage an adverse event) should ideally be taken

Table 2. WHO grouping of anti-TB drugs prescribed for longer MDR-TB regimens

Group A: all three drugs should be prescribed	Bedaquiline Levofloxacin or moxifloxacin Linezolid
Group B: all three drugs should be included	Clofazimine Cycloserine or terizidone
Group C: should be prescribed to complete the regimen, and when group A and B cannot be administered	Amikacin (or streptomycin) Delamanid Ethambutol Ethionamide or prothionamide Imipenem–cilastatin or meropenem Pyrazinamide PAS

PAS: para-aminosalicylic acid.

within a team of experts with complementary competences (a consilium or similar body). National and international consilia are considered by WHO to be important in ensuring the best possible management of these difficult-to-treat cases and to prevent development of super-resistance.

Scale-up of culture and DST capacities, and the expanded use of high-technology assays for rapid determination of resistance (*e.g.* GeneXpert) are necessary if better control of MDR- and XDR-TB is to be achieved. The majority of resistant cases can be treated successfully if well-designed regimens are used and surgical options are

Table 3. High-burden countries for TB, MDR-TB and TB/HIV according to WHO absolute estimates

TB	**MDR-TB**	**TB/HIV**
Angola	Bangladesh	Angola
Bangladesh	China	Brazil
Brazil	DPR Korea	Cameroon
China	DR Congo	China
DPR Korea	Ethiopia	DR Congo
DR Congo	India	Ethiopia
Ethiopia	Indonesia	India
India	Kazakhstan	Indonesia
Indonesia	Kenya	Kenya
Kenya	Mozambique	Lesotho
Mozambique	Myanmar	Malawi
Myanmar	Nigeria	Mozambique
Nigeria	Pakistan	Myanmar
Pakistan	Philippines	Nigeria
Philippines	Russian Federation	South Africa
Russian Federation	South Africa	Thailand
South Africa	Thailand	Uganda
Thailand	Ukraine	UR Tanzania
UR Tanzania	Uzbekistan	Zambia
Viet Nam	Viet Nam	Zimbabwe

DPR: Democratic People's Republic; DR: Democratic Republic; UR: United Republic.

carefully considered. Nevertheless, the development of new (more effective and less toxic) drugs to treat patients is urgently needed. Adherence to internationally agreed standards of care and control practices is imperative.

However, to reduce the emergence of new cases of TB, it is strategically crucial to identify and treat the infected subjects at higher risk of developing TB. Isoniazid, administered for 6–12 months at a dosage of 5 $mg \cdot kg^{-1} \cdot day^{-1}$, decreases the probability of developing active disease by 60% for a 2-year period. Longer duration is correlated with a higher probability of hepatic dysfunction, irrespective of efficacy. Other alternative regimens prescribed are: isoniazid and rifampicin for 3–4 months, rifampicin for 3–4 months or weekly administration of isoniazid and rifapentine for 3 months.

Recently, more attention has been given to diagnosis and treatment of post-treatment sequaelae. As functional obstruction, restriction or mixed situations have been observed in ~30% of cases followed up in some centres, with hypoxaemia and impairment of quality of life, assessment of the patients' functional status and, eventually, pulmonary rehabilitation might be indicated. Further studies in high TB incidence countries should be implemented to better assess the real epidemiological impact of treatment and nontreatment sequaelae.

Prevention

In 1993, the United Nations stated that the global fight against TB must be a priority alongside the fight against HIV/AIDS and malaria. On this basis, in 1996, WHO issued a public health strategy called DOTS (directly observed treatment, short course). It was composed of five elements:

- political commitment to TB control
- bacteriological diagnosis through smear microscopy
- supervised and standardised short-course therapy
- supply of quality drugs without interruption
- standardised recording and reporting system for treatment outcomes

In 1996, a new WHO strategy called STOP-TB was issued to address the new emerging global epidemiological issues, such as MDR-TB and TB/HIV co-infection. Its aim was to meet the 2015 Millennium Development Goals (*i.e.* to halve TB prevalence and mortality compared to the data recorded in 1990) and to have a more comprehensive approach (*e.g.* involvement of the private sector, and engagement of the community and all healthcare providers). In 2014, the World Health Assembly approved the new WHO strategy, named the End-TB Strategy, based on three pillars:

- intensified and innovative TB care (*e.g.* management of LTBI and improved care of TB cases with comorbidities)
- development and enforcement of bold health system and social development policies (*e.g.* universal health coverage and social protection)
- promotion and intensification of research and innovation, focusing on new diagnostic, therapeutic and prevention tools

A relevant tool for the clinical and public health management of TB called the International Standards of Tuberculosis Care (ISTC) was developed by several stakeholders, coordinated by WHO, to provide evidence-based standards. The European Respiratory Society and the European Centre for Disease Prevention and Control adapted the ISTC to the European Union/European Economic Area, focusing on the goal of TB elimination.

Only one vaccine is currently available for the primary prevention of TB: it consists of a live attenuated strain of *M. bovis*, BCG, the efficacy of which has been proven in children for TB meningitis and miliary TB but not for PTB in endemic geographical areas. Safety concerns have been reported, particularly in HIV-positive patients. However, recent data retrieved from observational retrospective cohorts highlighted its preventative effectiveness.

The goal of the global elimination of TB, *i.e.* an incidence of new sputum smear-positive cases <1 per 1 million inhabitants, is difficult to achieve, the annual incidence decline being <2%, but the epidemiological scenario could improve with a multisector approach oriented by the evidence-based WHO strategies.

Further reading

- Barry PM, *et al.* (2016). Drug-Resistant Tuberculosis: A Survival Guide for Clinicians. 3rd Edn. San Francisco, Curry International Tuberculosis Center.
- Caminero LJ, *et al.* (2018). Treatment of drug-susceptible and drug-resistant tuberculosis. *In:* Migliori GB, *et al.*, eds. Tuberculosis (ERS Monograph). Sheffield, European Respiratory Society; pp. 152–178.
- Fitzgerald D, *et al.* (2005). *Mycobacterium tuberculosis*. *In*: Mandell GL, *et al.*, eds. Principles and Practice of Infectious Diseases. 6th Edn. Philadelphia, Churchill Livingstone; pp. 2852–2886.
- Frieden TR, *et al.* (2003). Tuberculosis. *Lancet*; 362: 887–899.
- Getahun H, *et al.* (2010). HIV infection-associated tuberculosis: the epidemiology and the response. *Clin Infect Dis*; 50: Suppl. 3, S201–S207.
- Hopewell PC, *et al.* (2006). International standards for tuberculosis care. *Lancet Infect Dis*; 6: 710–725.
- Knechel NA (2009). Tuberculosis: pathophysiology, clinical features, and diagnosis. *Crit Care Nurse*; 29: 34–43.
- Krutikov M, *et al.* (2018). New and repurposed drugs. *In:* Migliori GB, *et al.*, eds. Tuberculosis (ERS Monograph). Sheffield, European Respiratory Society; pp. 179–204.
- Lewinsohn DM, *et al.* (2017). Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. *Clin Infect Dis*; 64: 111–115.
- Mack U, *et al.* (2009). LTBI: latent tuberculosis infection or lasting immune responses to *M. tuberculosis*? A TBNET consensus statement. *Eur Respir J*; 33: 956–973.
- Migliori GB, *et al.* (2018). ERS/ECDC Statement: European Union standards for tuberculosis care, 2017 update. *Eur Respir J*; 51: 1702678.
- Nahid P, *et al.* (2016). Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis*; 63: e147–e195.
- Raviglione MC, *et al.* (2008). Tuberculosis. *In*: Fauci AS, *et al.*, eds. Harrison's Principles of Internal Medicine. 17th Edn. New York, McGraw-Hill Medical Publishing Division Inc., pp. 1006–1020.
- Sester M, *et al.* (2011). Interferon-γ release assays for the diagnosis of active tuberculosis: a systematic review and meta-analysis. *Eur Respir J*; 37: 100–111.
- Torrado E, *et al.* (2011). Cellular response to mycobacterial: balancing protection and pathology. *Trends Immunol*; 32: 66–72.
- University of Liverpool. HIV Drug Interactions. https://www.hiv-druginteractions.org/

- World Health Organization (2017). Global tuberculosis report 2017. Geneva, WHO.
- World Health Organization (2018). Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). Document WHO/CDS/TB/2018.18. Geneva, WHO.
- World Health Organization (2019). WHO consolidated guidelines on drug-resistant tuberculosis treatment. Document WHO/CDS/TB/2019.3. Geneva, WHO.

Tuberculosis in immunocompromised patients

Martina Sester

The incidence of active TB and attendant mortality is increased in patients with impaired cellular immunity, such as HIV-infected patients, solid organ and stem cell transplant recipients, patients receiving tumour necrosis factor (TNF)-α antagonists, and patients with end-stage renal failure. The relative risk for TB varies with the type of immunodeficiency (table 1) and mortality rates may be as high as 75%. This emphasises the particular importance of the cellular arm of the adaptive immune response for efficient control of *Mycobacterium tuberculosis*. In general, the presence of *M. tuberculosis*-specific cellular immunity is used as a surrogate marker for a previous contact. Consequently, a detailed knowledge of the pathomechanisms leading to increased incidence of TB in immunocompromised patients has also contributed to a better understanding of the principles of decreased test sensitivity in this vulnerable patient group.

Pathomechanisms of impaired TB control in immunocompromised patients

The general incidence of TB in immunocompromised patients may vary depending on the geographic location and may range from <1% to 15% in low- and high-prevalence countries, respectively. The relative risk of developing TB and the underlying pathomechanisms differ widely among the various groups due to differences in the cause and extent of immunodeficiency (table 1). The dramatic reduction in CD4$^+$ T-cell numbers in HIV-infected patients, in particular in those with AIDS, not only contributes to a severely impaired control of TB but also to a high percentage of false-negative diagnoses by immune-based tests. Similarly, immunosuppressive drug treatment after transplantation is associated with a decrease in T-cell function and may lead to a progressive decrease in *M. tuberculosis*-specific T-cell immunity over time. This not only facilitates reactivation but also contributes to a decreased sensitivity of immune-based testing. The uraemia-associated immunodeficiency syndrome in patients with end-stage renal failure has been characterised by a defect in co-stimulatory signals

Key points

- TB has a higher incidence among people with impaired cellular immunity.
- Diagnosis of TB is often delayed, owing to early lack of symptoms or unusual presentation.
- Immunocompromised patient groups with latent TB infection differ in their risk for progression towards TB.
- Preventive measures include targeted risk-adapted screening for latent TB infection and preventive chemotherapy prior to immunosuppressive treatments.

Table 1. Pathomechanisms and relative risk for TB in immunocompromised patients relative to persons without known risk factors (risk = 1)

Risk factor	Relative risk	Pathomechanism
HIV infection (AIDS)	100–170	Low CD4$^+$ T-cell counts
HIV infection (no AIDS)	50–100	Low CD4$^+$ T-cell counts
Transplantation	20–74	Decreased T-cell function and numbers
Chronic renal failure	10–25	Co-stimulation deficiency, chronic inflammation
TNF-α antagonists	2–9	Disintegration of granuloma

to antigen-specific T-cells, thereby contributing to an increased risk of infectious complications including TB. Finally, an increased incidence of active TB in patients receiving TNF-α antagonists is attributed to impaired T-cell function and failure to maintain the integrity of granulomata in latently infected patients.

Clinical presentation of active TB in immunocompromised patients

Active TB in immunocompromised patients can pose a number of challenges. Due to the impaired immune response, patients may be clinically oligosymptomatic in the beginning of active disease, and TB diagnosis is often delayed due to atypical presentations and more frequent extrapulmonary dissemination. Active TB is further aggravated by a significantly higher morbidity due to a more fatal course in the face of a weakened immune system. In addition, treatment is frequently complicated due to complex drug interactions and altered pharmacokinetics. The treatment of TB is also more difficult to manage in HIV-infected patients, as immune restoration induced by antiretroviral therapy may be responsible for a paradoxical worsening of TB manifestations, a phenomenon defined as immune reconstitution inflammatory syndrome (IRIS).

Diagnosis and treatment of active TB

In active TB suspects, diagnosis should follow a clinical algorithm that includes acid-fast bacilli (AFB) staining from two sputum samples and nucleic acid amplification (NAA) testing. In the case of negative results, bronchoalveolar lavage (BAL) should be obtained for microscopy, NAA and culture.

The first-choice treatment of immunocompromised patients with active TB does not differ from immunocompetent individuals, and should consist of a regimen including isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months (2HRZE), followed by a continuation phase with isoniazid and rifampicin for 4 months (4HR). Treatment of active TB may be complicated by interactions between antibacterial and immunosuppressive or antiretroviral drugs. Evidence in favour of extending the continuation phase is limited. Longer duration is recommended in patients with cavitation on their initial chest radiograph and/or positive cultures after 2 months of treatment, or in patients with involvement of the central nervous system.

Preventative approaches in immunocompromised patients

The increased risk of active TB in immunocompromised patients may result from an immunosuppression-induced reactivation of a previously acquired latent TB infection (LTBI) or new infections. While the extent of new infections is difficult to control as it largely depends on the overall prevalence of TB, the risk of progression from LTBI to active disease may be minimised by the early identification and treatment of latently infected patients. LTBI screening can be performed by the use of tuberculin skin testing (TST), where the cut-off of positivity is defined by the extent of immunodeficiency. At present, however, interferon-γ release assays (IGRAs) are more widely applied for the diagnosis of LTBI because of operational advantages, including internal positive controls. In addition, IGRAs have a higher specificity than TST and a higher sensitivity in immunocompromised patients. Current guidelines recommend regular screening for evidence of LTBI and, if possible, treatment prior to conditions of immunodeficiency, *i.e.* prior to transplantation or TNF-α antagonist therapy. Preventive chemotherapy is recommended in patients with a positive immune-based test (TST ≥5 or 10 mm depending on the type of immunodeficiency, or IGRA), with signs of TB on chest radiograph in patients with no or insufficient previous TB treatment, or in recent close contact with a patient with active TB in severely immunocompromised patients.

When evaluating the results of immune-based tests as a predictive measure for development of active disease, IGRAs are superior to TST for predicting development of TB in immunocompetent individuals. Nevertheless, the actual risk of progression to active disease determined by both TST and IGRAs is still overestimated and may differ according to the local prevalence of TB. The considerably low predictive value of LTBI testing in low TB incidence countries may be due to the fact that a positive immune response towards *M. tuberculosis* does not necessarily reflect a true infection with viable bacilli. Likewise, the predictive value for progression in immunocompromised patients is low and differs depending on the type of immunodeficiency. In a large study by the Tuberculosis Network European Trials group (TBnet) among various groups of immunocompromised patients in low TB incidence countries in Europe, the incidence of TB was shown to be highest among HIV-infected individuals with ongoing viral replication, whereas TB was absent or a rare event in all other risk groups, such as patients with rheumatoid arthritis or chronic renal failure, or solid organ or stem cell transplant recipients. Given these observations, the number needed to treat in immunocompromised patients is lowest in patients with HIV infection with ongoing viral replication and rather high in all other risk groups. In the latter groups, the number needed to treat may be reduced by targeted screening and treatment of patients with additional risk factors. Together, this may maximise effectiveness of preventive chemotherapy while minimising drug-related side-effects.

Conclusion

TB in immunocompromised patients is more frequent than in the general population, and morbidity and mortality are high. This high mortality is primarily due to delayed diagnosis and increased incidence of disseminated disease. Decisions for LTBI screening to guide preventive chemotherapy in immunocompromised patients needs integrative approaches that should consider clinical findings, the extent of immunodeficiency, individual risk factors and the overall prevalence of TB.

Further reading

- Barry CE 3rd, *et al.* (2009). The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. *Nat Rev Microbiol*; 7: 845–855.
- Bumbacea D, *et al.* (2012). The risk of tuberculosis in transplant candidates and recipients: a TBNET consensus statement. *Eur Respir J*; 40: 990–1013.

- Diel R, *et al.* (2011). Interferon-γ release assays for the diagnosis of latent *Mycobacterium tuberculosis* infection: a systematic review and meta-analysis. *Eur Respir J*; 37: 88–99.
- Getahun H, *et al.* (2015a). Latent *Mycobacterium tuberculosis* infection. *N Engl J Med*; 372: 2127–2135.
- Getahun H, *et al.* (2015b). Management of latent *Mycobacterium tuberculosis* infection: WHO guidelines for low tuberculosis burden countries. *Eur Respir J*; 46: 1563–1576.
- Girndt M, *et al.* (2001). Molecular aspects of T- and B-cell function in uremia. *Kidney Int Suppl*; 78: S206–S211.
- Horsburgh CR Jr, *et al.* (2015). Treatment of tuberculosis. *N Engl J Med*; 373: 2149–2160.
- Lange C, *et al.* (2016a). Clinical application of interferon-γ release assays for the prevention of tuberculosis in countries with low incidence. *Pathog Immun*; 1: 308–329.
- Lange C, *et al.* (2016b). Viral load and risk of tuberculosis in HIV infection. *J Acquir Immune Defic Syndr*; 71: e51–e53.
- Lönnroth K, *et al.* (2015). Towards tuberculosis elimination: an action framework for low-incidence countries. *Eur Respir J*; 45: 928–952.
- Mack U, *et al.* (2009). LTBI: latent tuberculosis infection or lasting immune responses to *M. tuberculosis*? A TBNET consensus statement. *Eur Respir J*; 33: 956–973.
- Rangaka MX, *et al.* (2012). Predictive value of interferon-γ release assays for incident active tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis*; 12: 45–55.
- Sester M, *et al.* (2010). Challenges and perspectives for improved management of HIV/*Mycobacterium tuberculosis* co-infection. *Eur Respir J*; 36: 1242–1247.
- Sester M, *et al.* (2012). TB in the immunocompromised host. *In*: Lange C, Migliori GB, eds. Tuberculosis (ERS Monograph). Sheffield, European Respiratory Society; pp. 230–241.
- Sester M, *et al.* (2014). Risk assessment of tuberculosis in immunocompromised patients. A TBNET study. *Am J Respir Crit Care Med*; 190: 1168–1176.
- Sester M, *et al.* (2015). Numbers needed to treat to prevent tuberculosis. *Eur Respir J*; 46: 1836–1838.
- Sester U, *et al.* (2009). Impaired detection of *Mycobacterium tuberculosis* immunity in patients using high levels of immunosuppressive drugs. *Eur Respir J*; 34: 702–710.
- Solovic I, *et al.* (2010). The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. *Eur Respir J*; 36: 1185–1206.
- World Health Organization (2018). Latent Tuberculosis Infection: Updated and Consolidated Guidelines for Programmatic Management. WHO/CDS/TB/2018.4. Geneva, World Health Organization. Available from: www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/

Extrapulmonary tuberculosis

Demosthenes Bouros and Argyrios Tzouvelekis

Extrapulmonary tuberculosis (EPTB) accounts for 30–50% of TB in health systems where there is universal free access to health. Prevalence varies significantly among countries depending on access to the health system, sex inequalities, difficulties in diagnosis and access to sophisticated tests. These reasons render the extrapolation of data for the coincidence of pulmonary tuberculosis (PTB) and EPTB difficult. HIV co-infection occurs in 10% of those with TB in most countries (but 74% in Africa) and low CD4 counts are associated with EPTB; 90% of patients with EPTB have no evidence of pulmonary infection on chest radiographs or in sputum cultures. Risk factors include HIV infection, tumor necrosis factor (TNF)-α inhibitors (*e.g.* infliximab), corticosteroids and malignancy. Most EPTB cases are due to primary disease, *i.e.* due to progressive infection in those who have no pre-existing immunity to mycobacterial antigens. Extrathoracic lymphadenitis is the only form of post-primary EPTB.

Diagnosis

EPTB is a great imitator and can easily be misdiagnosed. Symptoms of TB such as fever, weight loss, night sweats, general malaise and anorexia are nonspecific, and especially when there are no features of PTB, including cough, sputum or haemoptysis, the diagnosis is often delayed or even missed due to this nonspecific clinical presentation and poor performance of diagnostic tests. Signs of EPTB differ according to the tissues involved. The absence of any significant physical findings

Key points

- Extrapulmonary tuberculosis (EPTB) accounts for 30–50% of all TB cases in health systems where there is universal free access to health services.
- HIV co-infection occurs in 10% of TB cases and low CD4 counts are associated with EPTB.
- The diagnosis is often delayed or even missed due to nonspecific clinical presentation and poor performance of diagnostic tests.
- Apart from TB meningitis, the treatment of EPTB is the same as in pulmonary TB.
- Adjuvant corticosteroid therapy with dexamethasone or prednisone during the first 6–8 weeks for TB meningitis (reduces early mortality), TB pericarditis (prevents the need for pericardiectomy), renal TB (prevents ureteric stenosis) and in spinal cord compression TB (may reduce the neurological deficit) is advocated.

does not exclude active EPTB. Importantly, classic symptoms are often absent in high-risk patients, particularly those who are immunocompromised or elderly. Therefore, the first evidence to raise clinical suspicion are epidemiological risk factors, including close contact with active TB and current or previous residence in a high-incidence country. The combination of an immunological test, such as tuberculin skin testing (TST) or an interferon-γ release assay (IGRA), coupled with elevated inflammatory markers (erythrocyte sedimentation rate, C-reactive protein or high immunoglobulin/albumin ratio) without neutrophil leukocytosis recommends meticulous investigation for EPTB.

Novel molecular diagnostics, including nucleic acid amplification tests (NAATs) and antigen detection assays, have improved detection of TB and greatly accelerated detection of drug resistance. Multidrug-resistant TB and EPTB are increasing, highlighting the need for samples for NAATs and culture regardless of the lack of accessible sampling in many cases.

Treatment

Treatment of EPTB, in the majority of cases, is similar to PTB and consists of the four primary anti-TB drugs (isoniazid, rifampicin, ethambutol and pyrazinamide) for 2 months, and another 4 months with isoniazid and rifampicin in drug-susceptible cases. In certain cases including TB of the central nervous system (CNS), treatment for 1 year is recommended. In cases of TB meningitis, replacement of ethambutol with streptomycin is recommended (by the World Health Organization). Compounds with good cerebrospinal fluid (CSF) penetration are isoniazid, pyrazinamide, levofloxacin and ethionamide. Corticosteroids might also be needed in specific cases of CNS TB; TB pericarditis; TB iridocyclitis; TB lymphadenitis, especially in cases of enlarged lymph nodes pressing on or obstructing bronchi; immune reconstitution inflammatory syndrome; or life-threatening situations. PCR techniques hold promise for identification of the organism and drug-resistance genes.

Specific organ involvement

TB lymphadenitis

TB lymphadenitis represents a common presentation of EPTB in both children and adults. The most common sites are the anterior or posterior cervical and submandibular nodes. Lymph nodes remain enlarged for quite some time and are usually palpable at 2 months. Interestingly, lymph nodes can enlarge, regress and then enlarge again during the course of treatment. Enlargement after successful treatment is surprisingly common, and requires lymph node excision to exclude other diagnoses and to obtain sufficient material for culture. Nonetheless, retreatment is not required in the absence of a positive culture, even if dead bacilli are seen on staining of tissue sections.

Paradoxical reactions to TB treatment occur most commonly in association with HIV co-infection but are also a feature of cervical lymph node TB. Fine needle aspiration may aid in early diagnosis, avoiding fistula formation. Replacement of vitamin D, if low, may be considered.

Pleural TB

TB is the most common cause of one-sided pleural effusion, especially in exudative lymphocytic pleural effusion. In the industrialised world, pleural effusion with TB is more likely to be due to reactivation of TB disease whereas in the developing world it is more likely a manifestation of progressive primary disease. The pleural fluid is usually a straw-coloured exudate with lymphocytosis, protein concentration >30 $g \cdot L^{-1}$, lactate dehydrogenase often elevated even above 500 IU·L^{-1}, pH <7.40, and low glucose levels ranging between 3.33 and 5.55 mmol·L^{-1} or even <2.77 mmol·L^{-1} in a minority of cases. Large pleural effusions are frequently observed as a result of hypersensitivity reaction with low *Mycobacterium tuberculosis* numbers, making the diagnosis difficult.

Pleural fluid becomes culture positive in up to 75% of patients. Negative cytology for malignancy and the absence of neutrophils are important diagnostic elements. However, procedures such as pleural biopsy (for histology and culture) and medical thoracoscopy or video-assisted thoracoscopic surgery biopsy may be needed to set a firm diagnosis.

Tuberculous pleuritis is typically self limited. However, since 65% of patients with primary tuberculous pleuritis reactivate their disease within 5 years, empirical anti-TB treatment is usually begun pending culture results when sufficient clinical suspicion is present, such as an unexplained exudative or lymphocytic effusion in a patient with a positive finding (TST, QuantiFERON or pleural fluid deaminase). It should be highlighted that infectious TB usually occurs within the next 5 years if the effusion is not diagnosed and treated properly.

Pericardial TB

Pericardial TB is a potentially life-threatening situation, although rare (<1% of EPTB). TB pericarditis can present either acutely, with massive pericardial fluid accumulation causing cardiac tamponade, or subacutely, with constrictive pericarditis. Aspiration/drainage may control the acute situation but surgical intervention (forming an open pericardial window to prevent fluid re-accumulation) may also be required. Corticosteroids have a cardinal role for the avoidance of surgical interventions.

Miliary TB

Miliary TB refers to the resemblance of the multiple small (2 mm), discrete pulmonary opacities to millet seeds. It is a massive lymphohaematogeneous spread of *M. tuberculosis* throughout the body. It accounts for 3% of EPTB cases and is associated with immunodeficiency. Studies from South Africa have indicated that miliary TB is associated with acute respiratory distress syndrome in 50% of cases and thus is associated with increased mortality. In cases where the CSF indicates meningeal involvement, a more prolonged course of treatment is recommended.

Tuberculous meningitis and CNS TB

Altered mental status, neck stiffness, decreased level of consciousness, increased intracranial pressure and cranial nerve involvement can indicate tuberculous meningitis or tuberculoma. Altered mental status and decreased level of consciousness may especially alert the physician, and lead to early diagnosis and timely interventions. Patients may also present with a headache that has been either intermittent or persistent for 2–3 weeks. Altered mental status changes may progress to coma over a period of days to weeks. Thus, TB meningitis should be regarded as a medical emergency and if these conditions are suspected, a lumbar puncture for evaluation of the CSF is necessary. Application GeneXpert and an IGRA to the CSF, and negative results for other causes of a lymphocytic CSF (viral, *Listeria*, *etc.*) are of paramount importance. MRI is crucial for TB meningitis diagnosis. MRI is superior to CT both in terms of TB meningitis diagnosis by detecting basal enhancement in more patients and in terms of prognosis by detecting many more infarcts in strategic locations. Tuberculoma can be verified on MRI. Hydrocephalus and paralysis of the abducens nerve (VI cranial nerve palsy) can also be found. Early diagnosis and corticosteroid treatment may reduce mortality, but a 5-year follow-up of a Vietnamese cohort showed that there was no difference in eventual outcome between the steroid and nonsteroid groups. To this end, it seems that corticosteroids have an important role in the context of paradoxical enlargement of cerebral tuberculomas.

Skeletal TB

The most common site of skeletal TB involvement is the spine (Pott disease); symptoms include back pain or stiffness and may be serious. Lower-extremity paralysis is rare in spinal TB but occurs in up to half of patients with undiagnosed Pott disease. Progressive bone destruction may lead to vertebral collapse and kyphosis. Destructive cold abscesses may extend into adjacent ligaments and soft tissues (psoas abscess). Therefore, correct and early diagnosis is crucial. To achieve this, culture material must be achieved. Evaluation with CT scanning or MRI could provide fruitful insights, as different pathogens, including *Staphylococcus aureus* or *Escherichia coli*, abscesses have a different radiological appearance and a more rapid progression. Surgery for spinal instability is indicated if the angle at the lesion is >15°.

Tuberculous arthritis usually involves only one joint; the hips and knees are affected most commonly, followed by the ankle, elbow, wrist and shoulder. For peripheral joint disease, surgery is rarely indicated and should only be undertaken after 6 months of appropriate treatment.

Genitourinary TB

The kidneys are the most common site of genitourinary TB and are infected through haematogenous spread. From the kidneys, *M. tuberculosis* can spread to the renal tract, prostate and epididymis. Symptoms may include flank pain, dysuria and frequent urination. In men, genital TB may manifest as a painful scrotal mass, prostatitis, orchitis or epididymitis. Ovarian, tubal and testicular disease may result in infertility in ~10% of cases.

Renal TB is usually unilateral and rarely causes renal failure. Ureteric fibrosis and stricture formation may cause hydronephrosis, whereas TB of the bladder wall may lead to its fibrosis.

Urinalysis and urine cultures can be obtained for patients with genitourinary complaints. Although patients are often asymptomatic, significant pyuria and/or haematuria with no routine bacterial organisms (aseptic pyuria) mean that an early-morning urine culture for *M. tuberculosis* should be obtained. With regards to treatment, early application of corticosteroids may be critical for prevention of ureteric stenosis.

Gastrointestinal TB

Any site along the gastrointestinal tract may become infected. Symptoms of gastrointestinal TB are referrable to the infected site, and include nonhealing ulcers of the mouth or anus, difficulty swallowing, abdominal pain mimicking peptic ulcer, malabsorption and diarrhoea.

With regards to differential diagnosis, Crohn's disease is almost absent in sub-Saharan Africa and is also relatively rare in the Indian subcontinent compared to TB. An IGRA and TST are often used before anti-TNF treatment in Crohn's disease. In cases of positivity, efforts should be directed towards obtaining culture samples while at the same time, empirical TB treatment may be considered followed by assessment of any therapeutic response after 2 months.

Ocular TB

TB can affect any structure in the eye, presenting as keratitis, iridocyclitis, intermediate uveitis, retinitis, scleritis and orbital abscess. Choroidal tubercles and choroiditis are the most common ocular presentations of TB. Patients may complain of blurry vision that may or may not be associated with pain and red eye. Uveitis with a positive TST/IGRA should raise suspicion. Finally, the association of Eales disease, an autoimmune vasculitis of the eye requiring steroids, with TB infection is still controversial and debatable.

Further reading

- Bouros D. (2009). Pleural Disease. 2nd Edn. New York, Taylor and Francis CRC Press.
- Houston A, *et al.* (2014). Extrapulmonary tuberculosis. *Medicine*; 42: 18–22.
- Lawn SD, *et al.* (2013). Advances in tuberculosis diagnostics: the Xpert MTB/RIF assay and future prospects for a point-of-care test. *Lancet Infect Dis;* 13: 349.
- Miller FJW. (1981). *Tuberculosis in Children*. Edinburgh, Churchill Livingstone.
- Norbis L, *et al.* (2014). Challenges and perspectives in the diagnosis of extrapulmonary tuberculosis. *J Exp Rev Anti-infect Ther*; 12: 633–647.
- Rajasekaran S, *et al.* (2018). Spinal tuberculosis: current concepts. *Global Spine J*; 8: Suppl., 96S–108S.
- Thwaites GE, *et al.* (2004). Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *NEJM*; 351: 1741–51.

Latent tuberculosis

Jean-Pierre Zellweger

Individuals who are in close contact with a patient with a transmissible form of TB, usually smear-positive pulmonary TB, may inhale droplets containing mycobacteria, which settle in the airways and give rise to a local inflammatory reaction. The risk of infection is related to the concentration of mycobacteria in the air and the duration of contact. Some exposed individuals develop TB within a couple of weeks or months, others will control the incipient infection and stay, for a prolonged period (up to years), in a state of equilibrium called ‘latent TB infection’ (LTBI).

LTBI and risk of TB

Individuals with latent TB have no signs or symptoms of disease, and only immunological markers of a prior contact with mycobacteria. As latent TB is defined by the presence of an immunological reaction, some authors prefer the term ‘lasting TB immune response’, which does not suggest the persistence of mycobacteria. It is therefore impossible to know whether individuals with LTBI still harbour living mycobacteria. The only gold standard definition of TB infection is the development of the disease, which only happens in a minority of exposed individuals. Why and how the infected individuals will develop TB is unknown. Traditionally, estimates are that ~10% of infected individuals will develop TB, half of them within 2 years after infection, and 90% will never develop the disease. Recent studies tend to indicate that the risk in adults is lower, between 1% and 2% per year during the first years after infection,

Key points

- The risk of latent TB infection (LTBI) depends on the intensity and duration of exposure to a source case with untreated pulmonary TB.
- Some infected contacts will develop TB at a later time-point. Timely detection of infected contacts and preventive treatment of those at highest risk of reactivation is cost-effective and reduces the pool of future cases of active TB.
- Before prescribing preventive treatment, active TB should be excluded by a clinical examination, a chest radiograph and, if abnormal, by a bacteriological examination of sputum.
- The tests for the detection of latent infection are the tuberculin skin test and the interferon-γ release assays (IGRAs). The latter have the advantage of a greater specificity.
- Immunological tests for the detection of LTBI, particularly IGRAs, have a low positive predictive value but a high negative predictive value.

but some infected individuals have a higher risk of later reactivation than others (*e.g.* immunocompromised individuals, patients receiving immunosuppressive therapy and small children). As only a minority of contacts develop TB, there is a possibility that most contacts eradicate the mycobacteria but still retain an immunological marker of the infection, even in the absence of living mycobacteria.

Treatment of LTBI

As the persons in contact with a case of TB have a much higher risk of developing the disease in the future than the general population, particularly if they have a positive tuberculin reaction or a positive interferon-γ release assay (IGRA) test, the detection of LTBI among exposed contacts is important because a preventive treatment can reduce this risk. The search for latent infection among contacts and the prescription of preventive treatment may contribute to the control of the disease by reducing the pool of potential future cases. The currently recommended preventive treatments are 9 months of isoniazid and 4 months of rifampicin, or 3 months of a combination of isoniazid and rifampicin. Recently, the use of rifapentine and isoniazid once a week for 12 weeks has also been demonstrated to be very effective.

As the immunological reaction after the contact with mycobacteria needs several weeks to be complete, the proof of a recent sensitisation is usually not present before this time (the window period). Therefore, the search for latent infection is usually performed 6–8 weeks after the last contact. In some cases, where the progression from infection to disease may be rapid (such as immunocompromised contacts or children aged <5 years), a first test with a clinical examination must be performed as soon as possible after the last contact and repeated several weeks later if the results are negative. A test performed immediately after the last contact will usually indicate a prior sensitisation, and may be observed among contacts born in a region with high prevalence of TB and in elderly people, independently of recent contacts.

Tests for detection of LTBI

The tests used for the detection of latent infection are all indirect, and rely on the reaction between sensitised lymphocytes and antigens from *Mycobacterium tuberculosis*. The traditional test is the tuberculin skin test measuring the cutaneous reaction elicited by the intradermal injection of a mixture of antigens from *M. tuberculosis* cultures. New tests have been developed, measuring *in vitro* the release of cytokines (interferon-γ) by lymphocytes incubated with two specific antigens present in *M. tuberculosis* but absent in *Mycobacterium bovis* Bacille Calmette–Guérin (BCG) and in most nontuberculous mycobacteria (IGRAs). The *in vitro* tests are (at least) equally sensitive to the tuberculin test and have the advantage of greater specificity, therefore avoiding the false-positive skin reactions elicited by prior BCG vaccination or contact with nontuberculous mycobacteria.

Detection and management of LTBI

Traditionally, the search for LTBI was limited to individuals with a very high risk of infection (small children in contact with patients with smear-positive pulmonary TB) or very high risk of developing TB if infected (immunocompromised persons), and was performed only in low-burden countries. The aim of contact investigation was mainly to detect and treat contacts who already started to develop TB (secondary cases) among the relatives of patients with active TB. More recently, considering the unsatisfactory rate of decline in TB worldwide, the World Health Organization has extended the recommendations for the active search of infection to all contacts of patients with transmissible forms of TB, independent of age, and to all immunocompromised individuals, including patients receiving immunosuppressive therapy like anti-tumour necrosis factor medication. Other groups with an increased risk of exposure, infection and/or reactivation of TB if infected, like healthcare workers exposed to untreated cases of TB, young migrants from high-prevalence regions and prison inmates, could also be considered, if the local capacity is sufficient. The current guidelines reinforce the idea of decreasing the pool of future cases of TB, thus contributing to the acceleration of the decline of incidence. Screening for latent TB is now considered as one component of the global End TB Strategy, second to the detection and treatment of cases of active TB, and may contribute to the aim of TB elimination. Consequent implementation of detection and treatment of latent infection in children exposed to TB could have a major impact on children morbidity and mortality due to TB.

All persons at risk with immunological signs of infection (positive tuberculin skin test or IGRA) should have at least a chest radiograph for detecting signs of past or current TB. Before prescribing a preventive treatment in contacts with an abnormal chest radiograph, the presence of TB should be excluded by a bacteriological examination of sputum. The efficiency of the preventive treatment largely depends on the rate of treatment completion. Contacts of patients with multidrug-resistant TB must be managed with special care, based on the drug sensitivity of the strain of the source case.

Controversies and open questions

The active search for infection is frequently considered not to be cost-effective because a large number of infected individuals have to be prescribed a preventive treatment (with potential adverse events) to prevent one single case of TB in the future. Estimates vary between 30 and 35 based on a review but this number could be decreased to six if individuals risk factors are considered. One of the obstacles to the generalisation of screening and preventive treatment is the fact that the tests currently available have a low positive predictive value (only a small minority of infected people will develop TB). However, it has been clearly demonstrated that the tests, particularly the IGRAs, have a very high negative predictive value and that the exposed persons with a negative test result have a negligible risk of developing TB in the future, unless they are re-exposed and infected. A recent study has demonstrated that the risk of progression to TB is correlated with the size of the IGRA test reaction.

Furthermore, the efficacy of preventive treatment largely depends on therapeutic adherence, which may be insufficient if the infected person (who is, by definition, asymptomatic) and the treating physician are not convinced of the usefulness of the treatment. Some studies report very low rates of treatment completion, whereas others have demonstrated that good management can increase the completion rate to satisfactory levels, particularly if short-course regimens are prescribed.

Further reading

- Abubakar I, *et al.* (2018). Prognostic value of interferon-γ release assays and tuberculin skin test in predicting the development of active tuberculosis (UK PREDICT TB): a prospective cohort study. *Lancet Infect Dis*; 18: 1077–1087.
- Alsdurf H, *et al.* (2016). The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. *Lancet Infect Dis*; 16: 1269–1278.
- Altet N, *et al.* (2015). Predicting the development of tuberculosis with the tuberculin skin test and QuantiFERON testing. *Ann Am Thorac Soc*; 12: 680–688.

- Dodd PJ, *et al.* (2018). Potential effect of household contact management on childhood tuberculosis: a mathematical modelling study. *Lancet Glob Health*; 6: e1329–e1338.
- Erkens CG, *et al.* (2010). Tuberculosis contact investigation in low prevalence countries: a European consensus. *Eur Respir J*; 36: 925–949.
- Fox GJ, *et al.* (2013). Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J*; 41: 140–156.
- Fox GJ, *et al.* (2017a). Latent tuberculous infection in household contacts of multidrug-resistant and newly diagnosed tuberculosis. *Int J Tuberc Lung Dis*; 21: 297–302.
- Fox GJ, *et al.* (2017b). Preventive therapy for latent tuberculosis infection-the promise and the challenges. *Int J Infect Dis*; 56: 68–76.
- Landry J, *et al.* (2008). Preventive chemotherapy. Where has it got us? Where to go next? *Int J Tuberc Lung Dis*; 12: 1352–1364.
- Mack U, *et al.* (2009). LTBI: latent tuberculosis infection or lasting immune responses to *M. tuberculosis*? A TBNET consensus statement. *Eur Respir J*; 33: 956–973.
- Moran-Mendoza O, *et al.* (2010). Risk factors for developing tuberculosis: a 12-year follow-up of contacts of tuberculosis cases. *Int J Tuberc Lung Dis*; 14: 1112–1119.
- Saunders MJ, *et al.* (2017). A score to predict and stratify risk of tuberculosis in adult contacts of tuberculosis index cases: a prospective derivation and external validation cohort study. *Lancet Infect Dis*; 17: 1190–1199.
- Sester M, *et al.* (2015). Numbers needed to treat to prevent tuberculosis. *Eur Respir J*; 46: 1836–1838.
- Sterling TR, *et al.* (2011). Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*; 365: 2155–2166.
- Winje BA, *et al.* (2018). Stratification by interferon-γ release assay level predicts risk of incident TB. *Thorax*; 73: 652–661.
- World Health Organization (2012). Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. Geneva, WHO.
- World Health Organization (2014). Towards tuberculosis elimination: an action framework for low-incidence countries. Geneva, WHO.
- World Health Organization (2015). Guidelines on the management of latent tuberculosis infection. Geneva, WHO.
- World Health Organization (2018). Latent tuberculosis infection. Updated and consolidated guidelines for programmatic management. Geneva, WHO.
- Zellweger JP, *et al.* (2015). Risk assessment of tuberculosis in contacts by IFN-gamma release assays. A Tuberculosis Network European Trials Group Study. *Am J Respir Crit Care Med*; 191(10): 1176–1184.

Nontuberculous mycobacterial disease

Claudio Piersimoni

Nontuberculous mycobacteria (NTM) is the term indicating those *Mycobacterium* species that are different from *Mycobacterium tuberculosis* complex and *Mycobacterium leprae*, whose detection in clinical samples is almost invariably associated with disease. The most important features distinguishing NTM from *Mycobacterium tuberculosis* complex include a lower pathogenicity and the lack of human-to-human transmission. Recently, however, different clusters of *Mycobacterium abscessus* pulmonary disease reported in CF care facilities were shown to be acquired through transmission *via* fomites and long-lived infectious aerosols rather than from the environment. In this context, the widespread implementation of individual and cohort segregation of patients in CF centres (which have led to falling levels of methicillin-resistant *Staphylococcus aureus*, *Burkholderia*, and transmissible *Pseudomonas* infections), might be adopted to reduce or prevent the spread of *M. abscessus* infections. In addition, *in vitro* resistance to first-line anti-TB drugs is an important distinctive issue. The majority of the more than 170 recognised NTM species have been associated with disease in man or animals.

Epidemiology and pathogenesis

NTM are widely distributed in both natural and man-made environments; organisms can be found in soil and water with high isolation rates. Human disease is suspected to be acquired by environmental exposure and pulmonary infection is likely to be *via* the aerosol route.

The epidemiology of NTM disease has been difficult to determine because reporting is not mandatory in most countries and differentiation between infection/colonisation and disease may be problematic. However, recent studies have documented a steady increase of pulmonary disease among people with apparently normal immunity and minimal initial lung damage, with estimates ranging from 15.5 to 26.7 per 100 000 persons among those aged >50 years.

Key points

- Important features distinguishing nontuberculous mycobacteria from *Mycobacterium tuberculosis* complex include lower pathogenicity and lack of human-to-human transmission with the exception of rare cases of *Mycobacterium abscessus*.
- Diagnosis of nontuberculous mycobacteria disease requires both clinical and microbiological criteria to be met.
- Treatment is disappointing and is characterised by long duration and side-effects, leading to poor compliance.

Although much remains to be understood about the pathogenesis of NTM infections, the following is now well established.

- In HIV-infected patients, disseminated NTM infections occur only after the $CD4^+$ T-lymphocyte count has dropped below 50–70 cells·μL^{-1}.
- In HIV-uninfected patients, NTM infections may be associated with specific mutations in DNA repair mechanisms, interferon-γ and interleukin-12 synthesis and response pathways. Such changes could result in impairment of local pulmonary immunity thus allowing environmental NTM to colonise, infect and ultimately cause disease.

The most common clinical manifestation of NTM infection is pulmonary disease, but lymphatic, skin/soft tissue, osteoarticular and disseminated disease are also important.

Pulmonary disease

In immunocompetent subjects, NTM lung disease presents as one of the following clinical forms.

Cavitary lung disease

This pattern, which closely resembles pulmonary TB, involves the upper lobes of older males usually affected by a pre-existing destructive or obstructive lung condition such as pneumoconiosis, chronic bronchitis with emphysema (frequently associated with long-term heavy smoking) and bronchiectasis. Thin-walled cavities with scarce parenchymal infiltrate and a marked pleural thickening are characteristic. Signs and symptoms include chronic cough with sputum production and weakness. Dyspnoea, fever, weight loss and haemoptysis can also occur with advanced disease.

Nodular bronchiectasis

This pattern (also known as Lady Windermere syndrome) has been described in slender, elderly females with structural chest abnormalities (pectus excavatum, scoliosis and mitral valve prolapse) but no evidence of pre-existing lung disease. Indolent productive cough and purulent sputum are the most common presenting symptoms, while constitutional symptoms and haemoptysis are not common unless extensive disease is present. The radiographic findings include small nodular infiltrates and cylindrical bronchiectasis, predominately located within the middle lobe and lingula.

Hypersensitivity pneumonitis

A syndrome indistinguishable from hypersensitivity pneumonitis has been reported in subjects exposed to household water laden with *Mycobacterium avium* complex (MAC) organisms (hot tubs and medicinal baths). Full recovery usually occurs without any specific therapy (simply by avoiding further contact with contaminated solutions) but sometimes a combination therapy of steroids and antibiotics may be required.

In addition, NTM lung disease may be associated with the following conditions.

- HIV infection: although NTM are frequently recovered from respiratory specimens of HIV-infected subjects, extrapulmonary or disseminated disease are more likely to occur. The most relevant exception to this generalisation is *Mycobacterium kansasii*.
- Immune reconstitution disease: this clinical syndrome has been described in HIV-infected patients with poor immune function soon after the initiation of antiretroviral therapy. Antiretroviral therapy-induced restoration of the immune response may cause subclinical mycobacterial disease to manifest suddenly or be ‘unmasked’.

- Transplantation including both solid-organ and haematopoietic stem cell transplants: these infections generally occur late in the post-transplantation period, presenting as cutaneous lesions of the extremities, tenosynovitis, arthritis or pulmonary disease. Pleuropulmonary disease is the predominant manifestation among lung transplant recipients and also represents a significant proportion of NTM infections after heart transplant. The most common species reported to cause pulmonary disease include *M. kansasii*, *M. avium*, *M. abscessus* and *Mycobacterium xenopi*.
- Treatment with tumour necrosis factor-α antagonists
- CF

Laboratory diagnosis

Mycobacterial culture remains the cornerstone of definitive diagnosis. Therefore, appropriate, high-quality specimens properly collected from all patients with suspected NTM disease have to be sent to a certified laboratory. Due to the ubiquitous occurrence of NTM in the environment, the recognition of disease, as opposed to contamination of specimens or transient colonisation, may be difficult. While smear-positive samples strongly suggest an active disease, a single positive culture (especially with small numbers of organisms) does not suffice to set such a diagnosis. In this context, the American Thoracic Society has recently updated the criteria for the diagnosis of pulmonary disease caused by NTM (table 1).

It is necessary to fulfil all the above elements to establish a correct diagnosis. Although these criteria are derived from experience with MAC, it is reasonable to believe they would work with other species provided that contamination of clinical specimens and medical devices with environmental NTM (pseudo-infection) has been excluded. Today, the combined use of automated liquid culture for detection and drug susceptibility testing plus the use of genetic probe technology for identification of mycobacteria is mandatory in all laboratories wishing to perform mycobacteriology.

Treatment

Treatment regimens for NTM disease are still largely undefined and outcome remains disappointing despite considerable upgrading in mycobacteriology and the availability of some new antimicrobials. Many patients fail therapy and more than one-half will have either recrudescent disease or new infection after completing these treatments. Apart from the intrinsic resistance of the most commonly isolated

Table 1. American Thoracic Society criteria for diagnosis of pulmonary disease caused by NTM

Clinical criteria (both required)
Pulmonary symptoms, cavitary or noncavitary lung disease
Appropriate exclusion of other causes for the disease
Microbiological criteria (only one required)
Positive culture results from at least two separate expectorated sputum samples
Positive culture results from at least one bronchial wash or lavage
A transbronchial or lung biopsy showing granulomata and/or AFB and positive culture for NTM
Biopsy showing granulomata and/or AFB and one or more sputa or bronchial washing that are culture-positive for NTM

AFB: acid-fast bacilli.

organisms (MAC and *M. abscessus*) to multiple antimicrobial agents, treatment success is impaired by the long duration of regimens, their side-effects and drug interactions, which prevent patients from full compliance (table 2). In addition, a remarkable drawback of the existing regimens is the lack of standardised and generally applied outcome measures.

Table 2. Clinical and radiography features of pulmonary infections caused by the most frequently encountered NTM

Species	Pathogenicity	Outcome	Radiography findings	Treatment months
MAC	Intermediate	Poor/fair	Upper lobe cavitations	Clarithromycin, ethambutol, rifampicin (12 months)[#], amikacin (3 months)
			Middle lobe bronchiectasis	Clarithromycin, ethambutol, rifampicin (12 months)[#]
M. abscessus	Intermediate	Poor	Multilobar interstitial and nodular lesions	Clarithromycin, amikacin, imipenem, tigecycline (6–12 months), surgical resection
M. kansasii	High	Good	Upper lobe cavitations	Rifampicin, isoniazid, ethambutol (12 months)[#]
M. malmoense	High	Fair	Upper lobe infiltrates	Rifampicin, ethambutol, clarithromycin (12 months)[#]
M. xenopi	Low	Poor	Upper lobe cavitations and nodules	Clarithromycin, rifampicin, ethambutol, moxifloxacin (12 months)[#]
M. szulgai	High	Good	Upper lobe cavitations	Rifampicin, isoniazid, ethambutol, pyrazinamide (12 months)[#]
M. simiae	Low	Poor	Upper lobe cavitations and nodules	Clarithromycin, moxifloxacin, co-trimoxazole (12 months)[#]

[#]: after culture conversion. Reproduced and modified from Piersimoni *et al.* (2008) with permission from the publisher.

Further reading

- Baldwin SL, *et al.* (2019). The complexities and challenges of preventing and treating nontuberculous mycobacterial diseases. *PLoS Negl Trop Dis*; 13: e0007083.
- Brown-Elliott BA, *et al.* (2012). Antimicrobial susceptibility testing, drug resistance mechanisms, and therapy of infections with nontuberculous mycobacteria. *Clin Microbiol Rev*; 25: 545–582.
- Clinical and Laboratory Standard Institute (2018). Laboratory Detection and Identification of Mycobacteria. 2nd Edn. M48. Wayne, PA, CLSI.
- Clinical and Laboratory Standard Institute (2018). Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes. 3rd Edn. M24. Wayne, PA, CLSI.
- Doucette K, *et al.* (2004). Nontuberculous mycobacterial infection in hematopoietic stem cell and solid organ transplant recipients. *Clin Infect Dis*; 38: 1428–1439.
- Field SK, *et al.* (2006). Lung disease due to the more common nontuberculous mycobacteria. *Chest*; 129: 1653–1672.
- Fujita G, *et al.* (2007). Radiological findings of mycobacterial diseases. *J Infect Chemother*; 13: 8–17.
- Glassroth J (2008). Pulmonary disease due to nontuberculous mycobacteria. *Chest*; 133: 243–251.
- Haworth CS, *et al.* (2017). British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease. *BMJ Open Resp Res*; 4: e000242.
- Mangione E, *et al.* (2001). Nontuberculous mycobacterial disease following hot tub exposure. *Emerg Infect Dis*; 7: 1039–1042.
- Piersimoni C, *et al.* (2008). Pulmonary infections associated with non-tuberculous mycobacteria in immunocompetent patients. *Lancet Infect Dis*; 8: 323–334.
- Tortoli E (2003). Impact of genotypic studies on mycobacterial taxonomy: the new mycobacteria of the 1990s. *Clin Microbiol Rev*; 16: 319–354.

Pathology and molecular biology of lung cancer

Verena Tischler, Sylvie Lantuejoul, Lénaïg Mescam-Mancini,
Barbara Burroni and Anne McLeer-Florin

Lung cancer prognosis is poor, with a global survival rate, all stages combined, of ~15%, mainly because most cases are surgically unresectable at the time of diagnosis. However, the discovery in 2004 of *EGFR* (epidermal growth factor receptor) mutations in a subset of adenocarcinomas, leading to a specific clinical response to tyrosine kinase inhibitors (TKIs), has raised high hopes towards development of targeted therapies. Lung tumours in nonsmokers are the seventh cause of death by cancer worldwide and are more frequently observed in women, especially in Asia. These tumours are characterised by the presence of a 'driver' mutation – translocation or amplification of an oncogene – leading to constitutive stimulation of cell proliferation and antiapoptotic signalling pathways in the tumour cells (figure 1). In addition to histopathological diagnosis, molecular classification of all types of lung cancer have now been proposed and will lead to further development of specific therapies.

Molecular testing in lung cancer

However, taking into account the genomic evolution of all types of lung cancer, multiplex genomic testing is the first choice for the detection of genomic alterations in lung cancer. Compared with single-gene hotspot testing for predictive markers, targeted next-generation sequencing (NGS) solves the disadvantages of consecutive biomarker testing. Targeted NGS workflows provide short turnaround times, high sensitivity to detect predictive genomic alterations and need only tiny amounts of tumour tissue (10–40 ng DNA depending on panel and platform). Biological and clinical interpretation of NGS results for nonstandard molecular findings should be performed in an interdisciplinary team of molecular pathologists, molecular biologists, computational biologists, pneumologists, oncologists and human geneticists. The quality and validity of molecular results should be assured by regular successful participation in round robin trials. In addition, consensus statements, for example, of the College of American Pathologists/International Association for the Study of Lung Cancer and the National Comprehensive Cancer Network, should be considered. Harmonisation of molecular testing, reporting of molecular findings and clinical–biological interpretation is important to achieve comparable results in

Key points

- Lung cancer prognosis is poor, most cases being surgically unresectable at the time of diagnosis.
- Driver mutations, translocations or amplifications are involved in lung oncogenesis, and have led to a molecular classification of lung tumours.

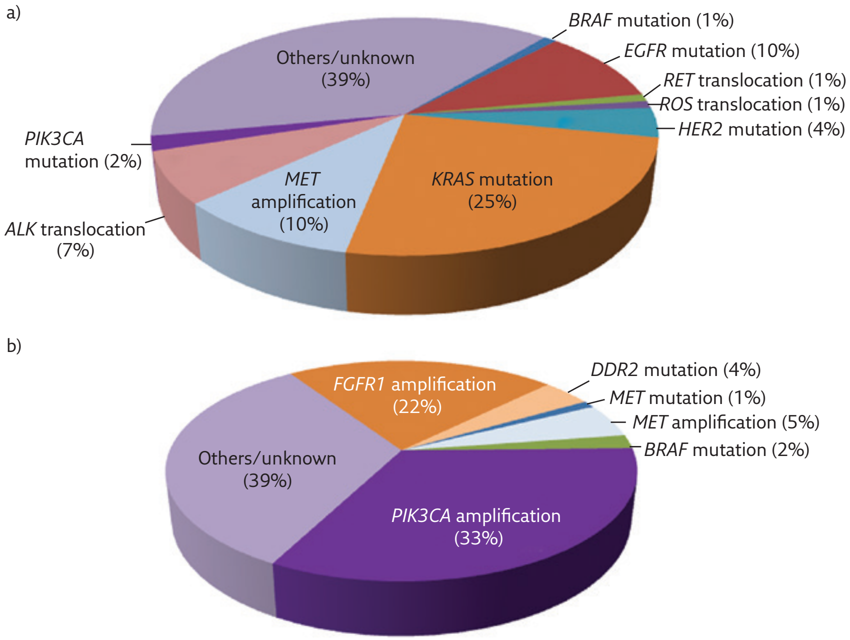


Figure 1. Druggable genetic abnormalities (mutation, amplification and rearrangement) in pulmonary a) adenocarcinomas and b) squamous cell carcinomas in Caucasian patients.

molecular diagnostics of lung cancer. One recent example for this is the efforts within the German consortium National Network Genomic Medicine (www.nngm.de).

ErbB family

The ErbB family comprises EGFR (also known as ErbB1 or human epidermal growth factor receptor (HER)1), ErbB2 (HER2 or Neu), ErbB3 (HER3) and ErbB4 (HER4).

EGFR gene mutations lead to activation of the Ras/mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K)/AKT downstream pathways. These mutations are found in 50% of adenocarcinomas in Asian patients and in only 15% of Caucasian patients. They mostly arise in nonsmoking women with papillar or lepidic adenocarcinomas, according to the new World Health Organization classification of lung adenocarcinoma, that are thyroid transcription factor (TTF)1 positive. In 85% of cases, these activating mutations correspond to a deletion in exon 19 (39%) or a point mutation (L858R) in exon 21 (46%), and confer sensitivity to the EGFR TKI gefitinib (marketed as Iressa by AstraZeneca, London, UK) and erlotinib (Tarceva; Genentech-Roche, San Francisco, CA, USA), which are US Food and Drug Administration (FDA)-approved for the treatment of mutated metastatic non-small cell lung carcinomas (NSCLCs). More recently, second- and third-generation EGFR TKIs have been developed. In the FLAURA trial, the third-generation EGFR TKI osimertinib resulted in an improved progression-free survival and less toxicity compared with first generation EGFR TKI.

Conversely, insertion in exon 20 is correlated with primary resistance to EGFR TKIs, and the T790M mutation is associated with secondary resistance. For treatment of tumours with T790M mutations, third-generation EGFR TKI like osimertinib and rociletinib irreversibly bind to EGFR to overcome resistance. Interestingly, *EGFR* T790M mutations can rarely occur as germline mutations. Antibodies raised against the exon 19-deleted form (del746–750) (clone 6B6; Cell Signaling Technology (Danvers, MA, USA) monoclonal antibody (mAb) 2085) and the exon 21-mutated form (L858R) (clone D38B1; Cell Signaling Technology mAb 3197) were developed for diagnosis by immunohistochemistry, with sensitivities ranging from 40% to 100% and specificities from 88% to 100%. Due to the large variety of predictive markers in lung cancer, multiplex assays and especially NGS applications are advantageous to save time and tissue. In addition, in clinical situations facing resistance to EGFR TKIs, NGS is a valuable tool to find the resistance mechanism. Typical resistance mechanisms of *EGFR*-mutated lung adenocarcinoma under EGFR TKI therapy are the development of *EGFR* T790M mutations, of *MET* or *HER2* amplifications, epithelial-to-mesenchymal transition (EMT), transition to small cell lung cancer subtype (through loss of tumour suppressor genes *TP53* and *RB1*) and *KRAS* mutations.

Another newly described mechanism of resistance to third-generation EGFR TKIs is C797S combined with T790M mutation *in trans*. These tumours remain sensitive to a combination of first- and third-generation TKIs but when both mutations occur *in cis*, EGFR TKI do not suppress activity. If only C797S is mutated, without T790M, the tumour cells are resistant to third-generation EGFR TKIs while sensitive to first-generation EGFR TKIs.

Mutations of *HER2* and *HER4* are rare (2–4%). *HER2* mutations (mainly insertions in exon 20 but also point mutations in exons 8, 17 and 19) are described as (likely) activating mutations. *HER2* amplification does not coincide with activating *HER2* mutations in lung cancer. Several efforts have been made to treat lung cancer patients with *HER2* mutations with HER2 antibodies or small molecule inhibitors showing promising results for this rare mutational subtype of lung cancer.

KRAS *and* BRAF

KRAS mutations are observed in up to 30% of adenocarcinomas. *KRAS* and *EGFR* mutations are mutually exclusive, and *KRAS* mutations are associated with a resistance to EGFR TKIs.

BRAF is a downstream effector of *RAS*. The *BRAF* V600E mutation is the most frequent (50%), followed by G469A (39%) and D594G (11%). They are observed in 3% of NSCLCs. Mutations other than V600E are more common in smokers; V600E is more common in women with micropapillar adenocarcinoma of poor prognosis. Treatment option for *BRAF* mutated lung cancer is a combination of BRAF and MEK (MAPK kinase) inhibitors.

ALK

In 2007, *ALK* (anaplastic lymphoma kinase) (chromosome 2p23) and *EML4* (echinoderm microtubule-associated protein-like 4) (2p21) gene rearrangement was identified in NSCLC. Other *ALK* fusion partners have been reported, such as *TFG* (TRK-fused gene), *KIF5B* (kinesin family member 5B) and *KLC1* (kinesin light chain 1). These rearrangements are observed in 3–7% of NCSLCs, and are mutually exclusive with *EGFR* and *KRAS* mutations. Patients with *ALK* rearrangement are often young, light smokers or nonsmokers at an advanced stage with frequent pleural localisations. *ALK*-positive tumours are mostly TTF1-positive adenocarcinomas with signet-ring cells. A favourable response with the FDA-approved, small-molecule ALK and MET inhibitor crizotinib has been shown for *ALK*-rearranged lung adenocarcinomas. Due to significantly better clinical results, next-generation ALK TKIs like alectinib now are the first choice

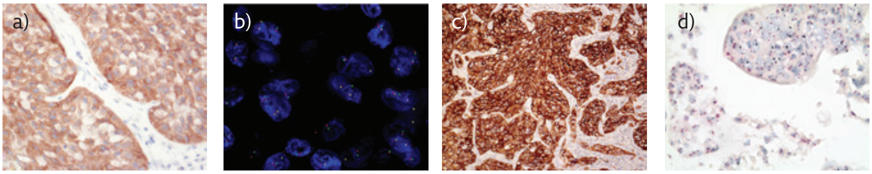


Figure 2. Examples of ALK and c-Met changes in NSCLC. a) Immunohistochemical expression of ALK fusion protein (Abcam clone 5A4). b) ALK gene rearrangement demonstrated by break-apart FISH (Vysis LSI ALK Dual-Color Break Apart Rearrangement Probe; Abbott Molecular, Des Plaines, IL, USA) showing typical split signals (red and green) in the same ALK-rearranged tumour as in a). c) Immunohistochemical expression of c-Met protein (clone SP44; Ventana Medical Systems, Oro Valley, AZ, USA). d) MET gene amplification demonstrated by SISH (silver in situ *hybridisation) (black: MET gene; red: chromosome 7 centromere) (Ventana Medical Systems).*

of therapy. FISH (fluorescence *in situ* hybridisation) was the gold-standard technique for diagnosis but since this technique is costly and time-consuming, pre-screening by immunohistochemistry has been suggested (figure 2a and b) with two antibodies (clone 5A4 (Abcam, Cambridge, UK) and D5F3 (Cell Signaling Technology)) with high sensitivities and specificities (92–100% and 99–100%, respectively). However, it has recently been shown that the exact *ALK* gene fusion is of importance for prediction and prognosis, with *ALK* variant V3 being a high-risk variant. As for mutational analysis, the application of multiplex techniques by NGS allows the identification of different binding partners and parallel analysis of a high number of relevant gene fusions. Typical mechanisms of secondary resistance are secondary point mutations, *ALK* gene amplification, *KIT* amplification, *KRAS* mutation, MAPK pathway mutation, activation of the insulin-like growth factor-1 receptor pathway and EMT.

ROS1 *and* RET

ROS1 (c-Ros oncogene 1, 6q22) rearrangements have been detected in 0.9–1.7% of NSCLCs and *RET* (Ret proto-oncogene, 10q11.2) rearrangements are observed in 1.2% of adenocarcinomas. Both types of rearrangements arise in young, light smoking or nonsmoking patients with adenocarcinomas, and seem to be mutually exclusive with *EGFR* mutations or *ALK* rearrangements. Crizotinib is the treatment option for *ROS1*-rearranged tumours. For *RET*-rearranged lung adenocarcinoma, the efficacy of multikinase inhibitors has been studied, which show a response rate of 18–37%.

MET

In lung cancer, the c-Met pathway, including PI3K/AKT/mammalian target of rapamycin (mTOR), Ras/MEK/MAPK, Src and STAT (signal transducer and activator of transcription), is activated either *via* ligand (hepatocyte growth factor) or receptor overexpression, *MET* gene amplification, mutations, or alternative splicing. Various scores for c-Met overexpression and *MET* amplification have been proposed (figure 2c and d). *MET* amplification seems to be correlated with a poor outcome, and c-Met phosphorylation with the development of brain metastases and primary and acquired resistance to EGFR TKIs. *MET* inhibitors might be a therapy option for patients with *MET* amplifications and exon 14 skipping mutations.

PIK3CA

The *PIK3CA* gene (PI3K catalytic subunit α) is mutated in 3.6% of squamous cell carcinomas (SCCs) and 2% of adenocarcinomas with an acinar or papillary histology.

Mutations affect exons 9 and 20, and amplification of the 3q25–27 genomic region containing *PIK3CA* (3q26) is detected in 10% NSCLC. In SCC, 3q26 amplification is reported in 40% of cases. These mutations or amplifications are not exclusive with those of *EGFR* and *KRAS*. Various PI3K inhibitors are under development, some also targeting mTOR. Whether the PI3K inhibitor alpelisib, recently approved for breast cancer by the FDA, will also achieve benefits for *PIK3CA*-mutated lung cancer remains to be answered.

FGFR1

Amplification of *FGFR1* (fibroblast growth factor receptor 1, 8p12) has recently been discovered in 20% of SCCs and 3.4% of adenocarcinomas. The clinical significance of FGFR1 inhibition and co-occuring genomic alterations is currently under further investigation.

Immunotherapy

Immunoediting is the response of the immune system to tumour cells. It is divided into three phases:

- Elimination
- Equation
- Escape

During elimination, tumour cells are eliminated by innate and adaptive immune responses. During the equation phase, tumour cells that survived the elimination phase can acquire new genomic alterations that overcome the scope of immune response. During the escape phase, newly mutated tumour cells escape the immune response and can found new clinically evident tumours or tumour relapses. Mechanisms of immune evasion are loss of antigen expression, activation of immunosuppression and exploitation of so-called immune checkpoints. Mechanistically, the tumour cells like PD-1/PD-L1 inhibitors express programmed death ligand (PD-L)1 and PD-L2 on their surface to bind PD-1 receptors on T-cells, leading to their inactivation. Immune checkpoint inhibitors have become important therapeutic strategies for lung cancer treatment. Predictive immunohistochemical testing of PD-L1 expression of tumour cells and immune cells of the tumour microenvironment are routinely performed in stage IV lung cancer cases. Another helpful biomarker for immune therapy decision, tumour mutational burden, is currently under evaluation for clinical approaches.

Conclusion

Historically, lung cancer classification and treatment were based on tumour histology. The discovery of driver mutations in genes encoding tyrosine kinases have led to a molecular classification of lung tumours, allowing the emergence of a personalised, targeted therapy and improved outcomes.

Further reading

- Benedettini E, *et al.* (2010). Met activation in non-small cell lung cancer is associated with *de novo* resistance to EGFR inhibitors and the development of brain metastasis. *Am J Pathol*; 177: 415–423.
- Bergethon K, *et al.* (2012). *ROS1* rearrangements define a unique molecular class of lung cancers. *J Clin Oncol*; 30: 863–870.
- Cappuzzo F, *et al.* (2009). Increased *MET* gene copy number negatively affects survival of surgically resected non-small-cell lung cancer patients. *J Clin Oncol*; 27: 1667–1674.

- Cheng L, *et al.* (2012). Molecular pathology of lung cancer: key to personalized medicine. *Mod Pathol*; 25: 347–369.
- Feng Y, *et al.* (2012). MET signaling: novel targeted inhibition and its clinical development in lung cancer. *J Thorac Oncol* 7: 459–467.
- Heist R, *et al.* (2012). Genetic changes in squamous cell lung cancer: a review. *J Thorac Oncol*; 7: 924–933.
- Kitamura A, *et al.* (2010). Immunohistochemical detection of *EGFR* mutation using mutation-specific antibodies in lung cancer. *Clin Cancer Res*; 16: 3349–3355.
- McLeer-Florin A, *et al.* (2012). Dual IHC and FISH testing for *ALK* gene rearrangement in lung adenocarcinomas in a routine practice: a French study. *J Thorac Oncol*; 7: 348–354.
- Paik PK, *et al.* (2011). Clinical characteristics of patients with lung adenocarcinomas harboring *BRAF* mutations. *J Clin Oncol*; 29: 2046–2051.

Lung cancer: diagnosis and staging

Johan Vansteenkiste, Griet Deslypere and Dorothee Gullentops

Epidemiology

Lung cancer occurs through a complex multistage process that results from the combination of carcinogen exposure and genetic susceptibility (figure 1).

Each puff of cigarette results in the delivery of a mixture of carcinogens and toxic agents along with nicotine. More than 20 lung carcinogens form the link between nicotine addiction and lung cancer, including polycyclic aromatic hydrocarbons and nicotine-derived nitrosoaminoketone. Those genotoxic carcinogens, either directly or after metabolic activation, react with DNA to form covalently bound DNA adducts. Adduct formation can either lead to apoptosis or it can be removed by the nucleotide excision repair system, but it can also cause miscoding events in critical genes that can drive the process toward lung cancer. Lung cancers are indeed among the cancers with the highest numbers of somatic mutations. The most frequently encountered mutations are in *TP53* (a tumour suppressor gene) and *KRAS* (a promotor oncogene), which are both critical growth control genes. Greater exposure to genotoxic carcinogens will increase the probability of DNA damage and mutations, thus increasing the probability of lung cancer. Several co-carcinogens and inflammatory damage enhance the carcinogenicity induced by cigarette smoke.

A number of lifestyle and environmental factors have been associated with the development of lung cancer, of which cigarette smoking is the most important. Cigarette smoking with prolonged use accounts for ~80–90% of all lung cancers. Compared with nonsmokers (*i.e.* lifetime exposure of <100 cigarettes), smokers have a ~20-fold increase in lung cancer risk, depending on the duration of smoking and

Key points

- Lung cancer is the most common cause of cancer-related mortality worldwide for both males and females, with a global incidence of nearly 2 million cases per year. The term lung cancer, or bronchogenic carcinoma, refers to malignancies that originate in the airways or pulmonary parenchyma.
- The pulmonologist has a crucial role in obtaining tissue for diagnosis and molecular analyses.
- Lung cancer staging is a stepwise process of more general tests for all patients, and more dedicated tests for patients with the prospect of radical treatment. The 8th edition of the TNM staging system is used.
- Functional assessment is key for patients treated with curative intent.

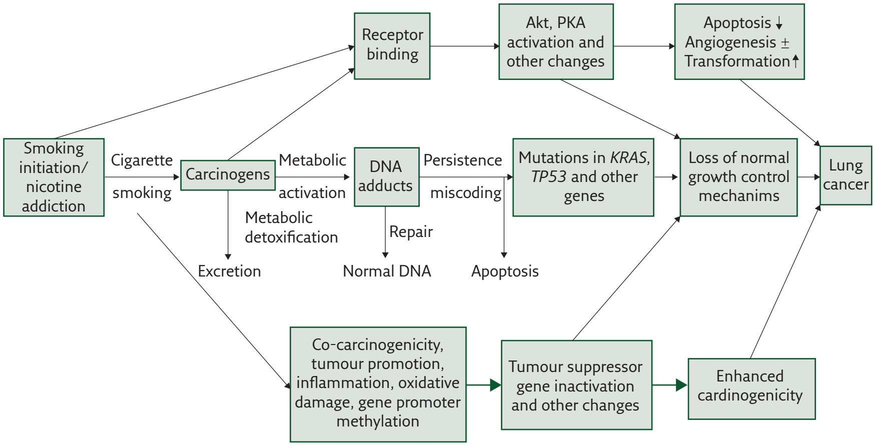

Smoking initiation/ nicotine addiction
Cigarette smoking
Carcinogens
Metabolic activation
DNA adducts
Persistence miscoding
Mutations in *KRAS*, *TP53* and other genes
Loss of normal growth control mechanims
Lung cancer
Receptor binding
Akt, PKA activation and other changes
Apoptosis ↓ Angiogenesis ± Transformation ↑
Metabolic detoxification
Excretion
Repair
Normal DNA
Apoptosis
Co-carcinogenicity, tumour promotion, inflammation, oxidative damage, gene promoter methylation
Tumour suppressor gene inactivation and other changes
Enhanced cardinogenicity

Figure 1. The multistep process leading from nicotine addiction to lung cancer. The central track is the main player. Each box and horizontal arrow in the central track represents a significant event or combination of events that drive the process towards cancer, while vertical arrows are protective. Reproduced from Hecht et al. *(2012) with permission.*

the number of cigarettes smoked per day. Cigarette smokers can benefit at any age from smoking cessation: as the period of abstinence from smoking increases, the risk of lung cancer decreases, although it remains elevated compared with never-smokers. In recent years, an increasing number of never-smoking patients have presented with lung cancer, often females with adenocarcinoma histology, especially in South-East Asia. Indeed, global statistics estimate that 15% of lung cancers in men and 53% in women are not attributable to smoking. Lung cancer in never-smokers is nowadays regarded as a distinct disease entity with other biology, natural history, molecular pathology and treatment possibilities, as compared to typical smoking-induced lung cancer. In particular, the outcome of these patients is far better because around half of them can be treated with very effective targeted therapy (see chapter on Chemotherapy and molecular biological therapy page 463).

Other risk factors for lung cancer are acquired lung diseases (COPD and pulmonary fibrosis) and environmental exposure (asbestos, radon, metals such as cadmium, chromium and nickel, arsenic, crystalline silica, polycyclic aromatic hydrocarbons, and ionising radiation including previous radiotherapy). Particularly worrisome is air pollution, as this affects everyone. Levels of fine dust, tar, soot and diesel exhausts can be important in urban air, and have been implicated in carcinogenesis. Although only weak to modest associations have been described at population levels, further research on the major cause(s) of lung cancer arising in never-smokers is needed.

Screening

As lung cancer is the largest contributor to mortality from cancer, identifying high-risk individuals in order to find lung cancer in an earlier stage and decrease the mortality rate is key. Historically, screening patients with radiographs showed no statistically significant mortality reduction compared to no screening. Molecular markers (in blood, sputum and bronchial washing) as screening tools are currently still under investigation, and therefore not to be used in clinical practice.

The benefit of yearly screening with low-dose CT has been demonstrated in the large North-American National Lung Cancer Screening Trial. Current or former smokers

(≥30 pack-years and smoking cessation <15 years ago), aged between 55 and 74 years, were assigned to either three annual chest radiograph (the control arm) or low-dose CT screenings. There was a relative reduction ratio in mortality due to lung cancer by 20% and a relative reduction in mortality due to any reason by 6.7%. The type of lung cancers that were found by screening were mostly early stage adenocarcinoma. Small cell lung cancer on the contrary was unfortunately never detected at an early stage. Based on these data, the US Preventive Service Task Force now recommends annual screening for lung cancer with low-dose CT in adults aged 55–80 years who have at least a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. In Europe, low-dose CT is not yet recommended in most countries, as questions on defining the optimal target groups and screening protocol, with implications on cost-effectiveness, deserve further study. Additional data will be generated soon from the large randomised NELSON study. This trial also studied the optimal interval of screening in order to minimise radiation exposure. A low-dose CT every 2 years seemed to be as good as a yearly screening, but a 2.5-year interval seemed to be too long because lung cancer was then clinically diagnosed between the screening time-points.

Contrary to a general misconception, lung cancer screening does not falsely reassure smokers, nor does it reduce their motivation to quit smoking. Indeed, engaging in CT lung cancer screening increased the likelihood of stopping smoking in the longer term, especially in cases when the CT scan showed abnormalities. Therefore, combining smoking cessation advice with low-dose CT screening is crucial.

Solitary pulmonary nodules

With the increasing use of CT for all types of diseases, asymptomatic patients with incidentally detected pulmonary nodules have become a real challenge. The proposed follow-up of these nodules can be based on the Fleischner criteria, which was entirely revised in 2017 and only indicated for incidentally detected solid and subsolid nodules. The recommendations take into account the size, number of nodules and other risk factors (smoking status, age, sex, race, localisation, spiculation, family history, pulmonary fibrosis, emphysema, multiplicity and environmental exposure). The recent revision reduced the number of unnecessary follow-up scans and proposed a range of times rather than a specific interval between two follow-up scans. The minimum threshold size for recommending follow-up is based on an estimated cancer risk in a nodule in the order of ≥1%: nodules of <6 mm in low risk patients do not require follow-up scans.

Several prediction models exist to manage nodules found by screening. The British Thoracic Society developed a risk prediction model for solitary pulmonary nodules. For nodules >8 mm, the validated Brock model is used to predict the risk of malignancy based on age, sex, family history, emphysema, size, upper lob localisation, nodule type, nodule count and spiculation. If the Brock model suggests a risk of >10%, a dedicated fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT is recommended. Herder's model (including PET) can than predict the risk of malignancy based on age, smoking status, nodule size, history of cancer, upper lobe localisation, spiculation and FDG avidity. If the risk remains >10% in this model, a biopsy is indicated.

For the rare pure ground-glass nodules (GGN), also called ground-glass opacities, predicting malignant changes is challenging. Although GGNs are generally known to grow slowly, the rate and pattern of growth are still unclear due to limited clinical experience. The clinical course of pure GGN is classified in three main ways: persistent pure GGN without or with increase in size, and change from a pure ground-glass to mixed solid/GGN. The latter two are suspect for malignant transition, in particular if the GGN size increases to >3 cm, or if a solid component develops in the GGN.

Clinical manifestations

The majority (at least 50%) of patients with lung cancer have advanced disease at clinical presentation, which reflects the frequent asymptomatic course of early stage lung cancer.

Symptoms due to the intrathoracic effects of the tumour are cough (central airway or pleural involvement), haemoptysis, chest pain, dyspnoea, hoarseness (laryngeal nerve involvement), superior vena cava syndrome (dilated neck veins and facial oedema) and Pancoast's syndrome (pain, Horner sign and hand muscle atrophy).

In addition, paraneoplastic effects of lung cancer are common: hypercalcaemia (nausea, lethargy, dehydration), syndrome of inappropriate antidiuretic hormone (hyponatraemia), hypertrophic osteo-arthropathy (clubbing, periostal proliferation of tubular bones), dermatomyositis, haematological manifestations (anaemia, leukocytosis, thrombocytosis), hypercoagulability, Cushing's syndrome (hyperkalemia, oedema, hypertension), and neurological syndromes (Lambert–Eaton). It is important to distinguish paraneoplastic effects from symptoms due to metastasis, as only the latter impede a radical approach. The most frequent sites of distant metastases are the liver (pain, constitutional symptoms), adrenal glands, bones (pain) and brain (headache, paresis, seizures). General symptoms such as anorexia, weight loss and asthenia are often present.

Pathology and molecular diagnosis

In case of a suggestive radiographic image of a central tumour, bronchoscopy is the appropriate test. A pathological diagnosis will be obtained in ~90% of cases, by means of forceps biopsy, bronchial brushing and/or washing.

Peripheral pulmonary lesions can be a diagnostic challenge. FDG-PET uptake or evolution over time can predict the risk of malignancy. For most lesions, pathological documentation is needed. For most lesions, pathological documentation is needed, either by true-cut biopsy under CT guidance or, if not possible, sometimes surgical sampling by video-assisted thoracoscopy. If the lesion is not too peripherally located, pathological diagnosis can nowadays be facilitated by using the guidance of minimally invasive techniques such as radial endobronchial ultrasound (EBUS)-guided biopsies, ultrathin bronchoscope (UTB) or virtual bronchoscopic navigation. The UTB method using a 3.0-mm ultrathin bronchoscope under EBUS or virtual bronchoscopic navigation guidance provides a high diagnostic yield without compromising safety. The diagnostic yield of the UTB method is higher than that of the thin (4 mm) bronchoscope with guided sheet.

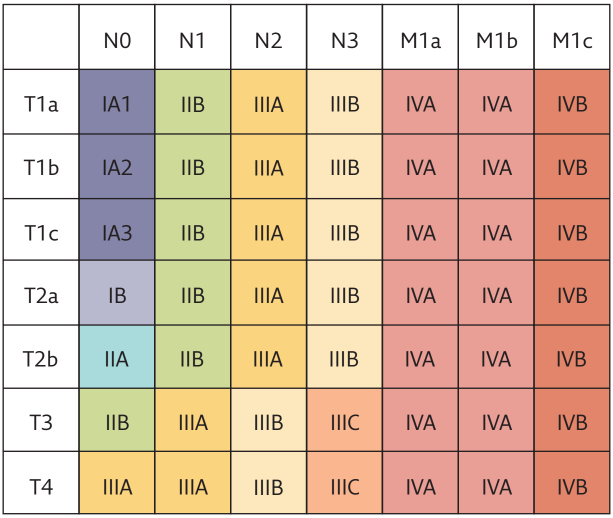
The major advances in the treatment of metastatic non-small cell lung cancer (NSCLC) imply an increasing demand for larger amounts of tissue for molecular pathology. Several predictive factors for treatment efficacy now need to be assessed, such as additional immunohistochemistry (ALK, PD-L1, ROS-1), in situ hybridisation testing (ALK, ROS-1, RET), or mutation testing by next generation sequencing (EGFR, BRAF, HER2). Therefore, it is important to maximise the number of biopsies at bronchoscopy and to make cellblocks of the cytological samples obtained at EBUS-transbronchial needle aspiration (TBNA), or to use larger core needles when taking a CT-guided transthoracic biopsy. Nowadays, EBUS-TBNA with a 21-Gauge needle can indeed provide histological specimens (EBUS-TBNA-H). The diagnostic yield of EBUS-TBNA-H specimens have been shown to be significantly better than classical EBUS-TBNA cytology specimens.

Staging

Staging, the process of determining the extent of lung cancer, is crucial for the prognosis and choice of treatment. The stage is defined by the international Tumour-Node-Metastasis (TNM) classification. Since January 2017, the TNM 8 classification has been validated and used in the staging of both NSCLC and small cell lung cancer. T status has to be evaluated on the lung windows of the CT scan and every centimetre counts. Stage IA is now divided into three different groups because of the 25% 5-year survival difference between IA1 and IA3 (figure 2 and table 1). Stage IIIc is a new category with survival rates in line with stage IV tumours. Multiple extrathoracic metastasis in one organ or extrathoracic metastasis in more than one organ (M1c) is now defined as stage IVB because of the clearly different prognosis compared to stage IVA in patients with M1a (intrathoracic metastases only) or M1b status (one single extrathoracic metastasis) (figure 3). The N status has not undergone revision.

For all patients, the minimal noninvasive staging will include a detailed medical history (smoking habits, occupational history, intra- and extrathoracic and paraneoplastic symptoms, performance status), a physical examination (*e.g.* careful auscultation and percussion may suggest the presence of atelectasis, pleural effusion or large airway obstruction, liver enlargement may indicate hepatic metastases, *etc.*), blood testing (blood cell count, kidney and liver function, ionogram) and a contrast-enhanced CT from the adrenal glands to the lung apex. According to symptoms and locoregional spread, a CT or MRI of the brain, a bone scintigraphy or other tests may be appropriate.

Patients with a potential for radical treatment (*i.e.* no evident metastatic disease or major comorbidity) will benefit from FDG-PET/CT, which improves staging of locoregional lymph nodes and distant spread (*e.g.* PET may indicate unexpected metastases in up to 20% of the patients).

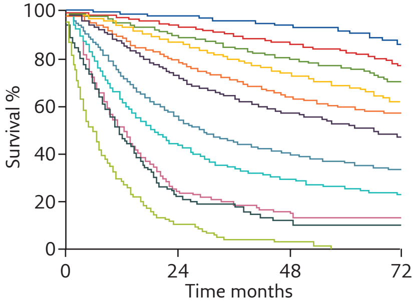


	N0	N1	N2	N3	M1a	M1b	M1c
T1a	IA1	IIB	IIIA	IIIB	IVA	IVA	IVB
T1b	IA2	IIB	IIIA	IIIB	IVA	IVA	IVB
T1c	IA3	IIB	IIIA	IIIB	IVA	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVA	IVB
T3	IIB	IIIA	IIIB	IIIC	IVA	IVA	IVB
T4	IIIA	IIIA	IIIB	IIIC	IVA	IVA	IVB

Figure 2. The IASLC lung cancer staging project: the stage grouping algorithm.

Table 1. The IASLC lung cancer staging project: description of the T-, N- and M-denominators

T: primary tumour	
Tx	Primary tumours cannot be assessed or tumour proven by presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
T1	Tumour ≤3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobular bronchus (*i.e.* not in the main bronchus)
T1a(mi) minimally invasive adenocarcinoma	
T1a	Tumour ≤1 cm in greatest dimension
T1b	Tumour >1 cm but ≤2 cm in greatest dimension
T1c	Tumour >2 cm but ≤3 cm in greatest dimension
T2	Tumour >3 cm but ≤5 cm or tumour with any of the following features: involves main bronchus regardless of distance from the carina but without involvement of the carina invades visceral pleura associated with atelectasis or obstructive pneumonias that extends to the hilar region, involving part or all of the lung
T2a	Tumour >3 cm but ≤4 cm in greatest dimension
T2b	Tumour >4 cm but ≤5 cm in greatest dimension
T3	Tumour >5 cm but ≤7 cm in greatest dimension or associated with separate tumour nodules(s) in the same lobe as the primary tumour or directly invades any of the other following structures: chest wall (including the partial pleura and superior sulcus tumours), phrenic nerve, parietal pericardium
T4	Tumour >7 cm in greatest dimension or associated with separate tumour nodule(s) in a different ipsilateral lobe then that of the primary tumour or invades any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body and carina
N: regional lymph node involvement	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)
M: distant metastasis	
M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural or pericardinal nodule(s) or malignant pleural or pericardinal effusions
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastasis in one or more organs



Proposed	Events/N	MST	24 month	60 month
IA1	68/781	NR	97%	92%
IA2	505/3105	NR	94%	83%
IA3	546/2417	NR	90%	77%
IB	560/1928	NR	87%	68%
IIA	215/585	NR	79%	60%
IIB	605/1453	66.0	72%	53%
IIIA	2052/3200	29.3	55%	36%
IIIB	1551/2140	19.0	44%	26%
IIIC	831/986	12.6	24%	13%
IVA	336/484	11.5	23%	10%
IVB	328/398	6.0	10%	0%

Figure 3. The IASLC lung cancer staging project: outcome according to the different clinical stages. MST: median survival time; NR: not reached. Reproduced from Goldstraw et al. *(2016) with permission.*

In non-metastatic patients, the exact definition of locoregional spread is crucial as it provides accurate information on the extent of the disease, which will help in selecting the best type of multimodality treatment (*i.e.* how to combine chemotherapy, surgery and radiotherapy), and determines the patient's prognosis. The risk of lymph node involvement increases with size of the primary tumour. The first visualisation of

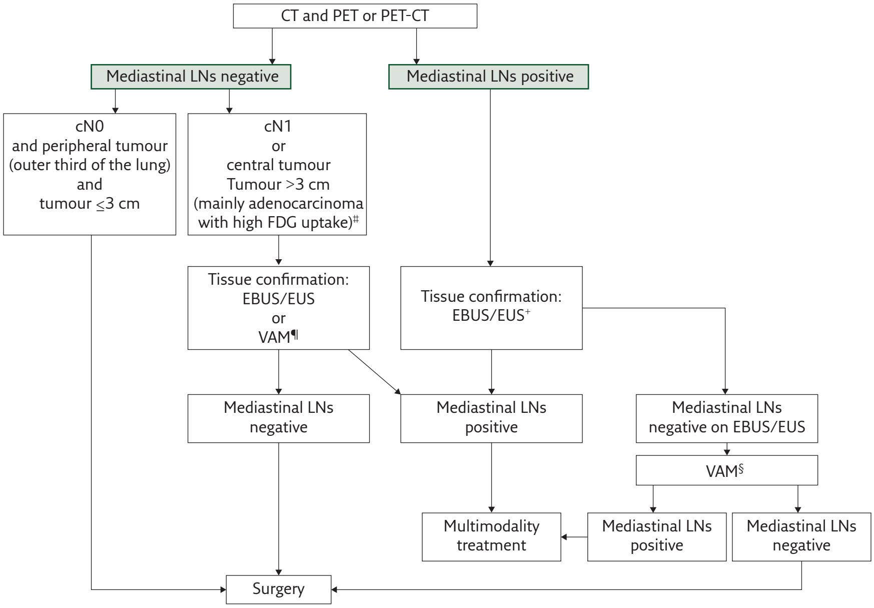

CT and PET or PET-CT
Mediastinal LNs negative
Mediastinal LNs positive
cN0 and peripheral tumour (outer third of the lung) and tumour ≤3 cm
cN1 or central tumour Tumour >3 cm (mainly adenocarcinoma with high FDG uptake)#
Tissue confirmation: EBUS/EUS or VAM¶
Tissue confirmation: EBUS/EUS+
Mediastinal LNs negative
Mediastinal LNs positive
Mediastinal LNs negative on EBUS/EUS
VAM§
Multimodality treatment
Mediastinal LNs positive
Mediastinal LNs negative
Surgery

Figure 4. European Society for Medical Oncology guidelines for mediastinal staging in early and locally advanced NSCLC. LN: lymph node; FDG: fluorodeoxyglucose; EUS: endoscopic ultrasound; VAM: video-assisted mediastinoscopy. #: in tumours with >3 cm (mainly in adenocarcinoma with high FDG uptake) invasive staging should be considered; ¶: depending on local expertise to adhere to minimal requirements for staging; +: endoscopic techniques are minimally invasive and are the first choice if local expertise with EBUS/EUS needle aspiration is available; §: due to its higher negative predictive value, in case of PET positive or CT enlarged mediastinal LNs, VAM with nodal dissection or biopsy remain indicated when endoscopic staging is negative. Nodal dissection has an increased accuracy over biopsy. Reproduced from De Leyn et al. *(2014) with permission.*

lymph node involvement is often by CT, but the value of CT to ascertain the nature of mediastinal lymph nodes is limited (pooled positive predictive value: 50%; negative predictive value: 80%). The addition of PET has improved these figures to 80% and 90%, respectively.

The recent revision of the European Society of Thoracic Surgeons guidelines for locoregional staging, also adopted by the European Society for Medical Oncology, provides a diagram for mediastinal staging (figure 4). Omission of pathologic assessment of lymph node spread and direct surgical resection is only recommended in tumours ≤3 cm and located in the outer third of the lung, with absence of enlarged lymph nodes on CT and FDG-uptake in lymph nodes on PET or PET/CT. This is based on a meta-analysis where the negative predictive value of PET-CT for tumours ≤3 cm was 94% compared to 89% for tumours >3 cm.

In tumours >3 cm, centrally located tumours, mediastinal lymph nodes with a short axis >10 mm on CT, or PET-positive hilar or mediastinal lymph nodes, PET/CT is not sensitive enough for reliable mediastinal lymph node mapping, and therefore preoperative invasive techniques are indicated if the patient is eligible for surgery. The historical standard was mediastinoscopy with a sensitivity of 78% of detecting mediastinal nodal disease. By first using less invasive techniques like EBUS/endoscopic ultrasound the sensitivity of detection of mediastinal nodal disease increases to 93%. However, as endoscopic staging may lead to false negative results in about 20% of the cases, completion with surgical staging is recommended in case of negative EBUS/endoscopic ultrasounds findings. By this, the detection of nodal metastases is optimised and the rate of unnecessary surgery is decreased (see chapter on Surgical treatment for lung cancer page 472). Moreover, this sequence is not associated with a greater rate of complications.

Another important advantage of using the endoscopic techniques upfront is that staging by mediastinoscopy can be reserved as the most accurate technique for assessment of lymph node staging after induction therapy.

In the specific case of clinical N1, the risk of having N2 disease is 19–30%. Recent data pointed out that endosonography missed N2 disease in 58% of the cases, while mediastinoscopy picked up at least one-half of these. Therefore, upfront mediastinoscopy is indicated in this particular situation.

In a geriatric population with stage IV NSCLC, the decision of who to treat and how to treat can be difficult. Performance status and age are important parameters but do not always cover the whole picture. In a comprehensive geriatric assessment, people are divided into fit, vulnerable and frail patients. In a recent study on the use of this comprehensive geriatric assessment, no better treatment failure-free or overall survival was noted, but all grades of treatment toxicity were reduced leading to fewer treatment failures as a result of treatment-related toxicity.

Functional assessment

All patients need an ECG and basic pulmonary function tests, such as FEV_1 and FVC, were performed. To determine the volume of lung that can be removed and to identify patients at risk for postoperative complications, each patient should undergo pulmonary function testing: lung volumes and D_{LCO}. Postoperative respiratory failure rarely occurs if the predicted post-resection FEV_1 and D_{LCO} are >30% to 40% of the normal values. Additional cardiopulmonary exercise testing with ergospirometry is indicated when baseline FEV_1 or D_{LCO} values are <80%. In this group, patients who reach their target heart rate and exercise capacity and who have a maximal oxygen consumption (maximal oxygen uptake) >20 mL·kg·min^{-1} are less likely to have postoperative complications or mortality. If the maximal oxygen uptake is between 10 and 20 mL·kg·min^{-1}, quantitative pulmonary perfusion scanning may be used to calculate the estimated postoperative values more precisely and the proportion of lung that can be removed. Moreover, patients with a baseline oxygen saturation of <90%, those who have >4% drop in oxygen saturation at exercise testing, or those with arterial blood gas carbon dioxide tension >45 mm have a greater likelihood of postoperative complications.

Apart from pulmonary function evaluation, assessment of other comorbid conditions, such as heart disease (echocardiography and coronary tests), renal insufficiency, diabetes, *etc.*, may be warranted.

Follow-up

The highest risk of relapse is noted during the first 2 years after surgery. Recurrence is dominated by distant metastases, rather than local relapses. The risk then decreases and is nearly absent after 5 years.

The risk of developing a second primary lung cancer, however, exhibits a more uniform pattern over time, ranging from 1% to 6% per person per year, and does not diminish over time. The median 10-year risk of second primary lung cancer among survivors of lung cancer is 8.36%, but the estimated risk varies substantially (range 0.56–14.3%) when stratified by age, histology and extent of initial primary lung cancer in the final prediction model. Patient age at the time of initial primary lung cancer diagnosis was the most important factor in predicting a second primary lung cancer risk, followed by histology and extent of disease. The group aged ≥85 years had a median 10-year risk of 1.1%, whereas the age group aged 60–64 years had the highest median risk at 10.97%

In most guidelines, follow-up every 6 months for the first 2 years after surgery is advised, with yearly follow-up thereafter. The results of the first randomised trial comparing two follow-up regimens after resection for pathologic stage I, II, and IIIA NSCLC were presented recently. In that trial, patients were followed at months 6, 12, 18, 24, 36, 48 and 60 months after surgery with either limited tests (clinical and chest radiography, CT only on indication) or more extensive tests (clinical, plus thoraco-abdominal CT, plus bronchoscopy if non-adenocarcinoma histology). There was no overall difference in median survival between both arms, but survival was significantly better in patients without recurrence after 2 years, most probably because of better detection of relapses with a more indolent biology and of second primary lung cancers.

There are no dedicated studies on the follow-up of patients with advanced lung cancer, but a follow-up every 3 months is generally recommended.

Further reading

- Aberle DR, *et al.* (2011). Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*; 365: 395–409.
- Annema JT, *et al.* (2010). Mediastinoscopy *versus* endosonography for mediastinal nodal staging of lung cancer. A randomized trial. *JAMA*; 304: 2245–2252.
- Brunelli A, *et al.* (2009). ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J*; 34: 17–41.

- Callister ME, *et al.* (2015). British Thoracic Society guidelines for the investigation and management of pulmonary nodules. *Thorax*; 70: Suppl 2, ii1–ii54.
- Corre R, *et al.* (2016). Use of a comprehensive geriatric assessment for the management of elderly patients with advanced non-small cell lung cancer: the phase III randomized ESOGIA-GFPC-GECP 08-02 study. *J Clin Oncol*; 34: 1476–1483.
- De Leyn P, *et al.* (2014). Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. *Eur J Cardiothorac Surg*; 3: 787–798.
- Dooms C, *et al.* (2015). Endosonography for mediastinal nodal staging of clinical N1 non-small cell lung cancer: a prospective multicenter study. *Chest*; 147: 209–215.
- Goldstraw P, *et al.* (2016). The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*; 11: 39–51.
- Gomez-Caro A, *et al.* (2012). False-negative rate after positron emission tomography/computer tomography scan for mediastinal staging in cI stage non-small cell lung cancer. *Eur J Cardiothorac Surg*; 42: 93–100.
- Han SS, *et al.* (2017). Risk stratification for second primary lung cancer. *J Clin Oncol*; 35: 2893–2899.
- Hecht SS (2012). Lung carcinogenesis by tobacco smoke. *Int J Cancer*; 131: 2724–2732.
- Lou F, *et al.* (2013). Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. *J Thorac Cardiovasc Surg*; 145: 75–81.
- Macmahon H, *et al.* (2017). Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. *Radiology*; 284: 228–243.
- Oki M, *et al.* (2015). Ultrathin bronchoscopy with multimodal devices for peripheral pulmonary lesions. A randomized trial. *Am J Respir Crit Care Med*; 192: 468–476.
- Postmus PE, *et al.* (2017). Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*; 28: Suppl 4, iv1–iv21.
- Sun S, *et al.* (2007). Lung cancer in never smokers – a different disease. *Nat Rev Cancer*; 7: 778–790.
- Travis WD, *et al.* (2013). New pathologic classification of lung cancer: relevance for clinical practice and clinical trials. *J Clin Oncol*; 31: 992–1001.
- Vansteenkiste J, *et al.* (2010). Early stage NSCLC: challenges in staging and adjuvant treatment: evidence-based staging. *Ann Oncol*; 21: Suppl 7, 189–195.
- Westeel V, *et al.* (2017). Results of the phase III IFCT-0302 trial assessing minimal *versus* CT-scan-based follow-up for completely resected non-small cell lung cancer (NSCLC). *Ann Oncol*; 28: Suppl 5, https://doi.org/10.1093/annonc/mdx378.012.
- Yousaf-Khan U, *et al.* (2016). Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval. *Thorax*; 72: 48–56.

Chemotherapy and molecular biological therapy

Amanda Tufman and Rudolf M. Huber

Most patients with lung cancer present in advanced stages of disease and cannot be cured by surgery or radiation therapy. In metastatic disease, the focus of treatment is palliation of symptoms and maintenance of quality of life. Systemic treatment forms the basis of treatment in stage IV and can significantly improve symptoms, and improves both progression-free and overall survival. Systemic treatment comprises chemotherapy and 'targeted' therapies, as well as immunotherapy with checkpoint inhibitors. Whereas chemotherapy involves the use of substances with nonspecific

Key points

- Due to the interdisciplinary nature of lung cancer treatment, decision-making should take place within structured tumour boards.
- Performance status is an important parameter in treatment decision-making.
- The side-effects of chemotherapy vary between agents and should be taken into account during treatment planning.
- The side-effects of immunotherapy can be life-threatening and should be known and treated according to the guidelines.
- Endobronchial techniques are an important tool in the palliation of lung cancer patients.
- First-line treatment of advanced non-small cell lung cancer, adjuvant chemotherapy and chemotherapy for radiochemotherapy is mostly a platinum-based doublet.
- The individualisation of treatment based on histology and molecular biology, in particular the *EGFR* mutation and *EML4–ALK* fusion, is of increasing importance in non-small cell lung cancer. There are further actionable mutations which can be found by next generation sequencing.
- Immune checkpoint inhibitors are the preferred agent in recurrent non-small cell lung cancer and first-line for tumours with high PD-L1 expression. This will probably also be the case for the other non-small cell lung cancer tumours in combination with chemotherapy.
- Small cell lung cancer generally responds well to initial chemotherapy, but recurs almost always and early. The addition of thoracic radiotherapy and prophylactic cranial irradiation can improve the outcome in the treatment of small cell lung cancer.

cytotoxic and antiproliferative properties, molecular biological therapy aims at more specific targets that are usually more active than normal. Tumour cells can inhibit the normal immune reaction, in part by blocking the activity of T-cells. Immune checkpoint inhibitors remove this brake on T-cells, which enables them to destroy tumour cells.

Depending on the clinical situation, either a single chemotherapeutic agent or a doublet may be given. If the patient is fit enough for chemotherapy, a platinum-based doublet is used. Differences in tumour histology and molecular biology are increasingly taken into account when planning systemic therapy, in particular for nonsmall cell lung cancer (NSCLC). Immune checkpoint inhibitors can be given in recurrent NSCLC instead of chemotherapy. Pembrolizumab is licensed in first-line NSCLC and high PD-L1 expression. There is evidence that immune checkpoint inhibitors combined with chemotherapy improve progression-free and overall survival in patients whose tumours show little or no PDL-1 expression.

Chemotherapy

In earlier stages of disease, systemic chemotherapy can be curative when combined with local irradiation (radiochemotherapy) or surgery. Chemotherapy given after surgery is known as adjuvant chemotherapy; that administered before surgery is neoadjuvant or induction chemotherapy. Most chemotherapy is given in stage IV or recurrent disease. Generally, chemotherapy is administered intravenously, although some agents may be given orally. There are also circumstances in which chemotherapeutic agents may be administered locally (intrathecally or in the pleural space). Although most modern chemotherapeutic agents have milder side-effects than the older agents, side-effects remain problematic and include neutropenia, neuropathy, nephropathy, fatigue, hair loss, nausea and vomiting (table 1). There are specific guidelines regarding antiemesis, neutropenia and anaemia, which have to be followed.

How to treat a patient is dependent not only on the diagnosis itself but on the patient's comorbidities and overall medical condition, as well as on the overall prognosis and goal of treatment (table 2). Performance status scales attempt to standardise the assessment of a patient's general state of health; the Karnofsky scale and the World Health Organization/Eastern Cooperative Oncology Group scale are commonly used (table 3).

In most cases, the overall management of lung cancer involves a combination of chemotherapy, radiation, bronchoscopic intervention and surgery. For this reason, interdisciplinary tumour boards are an important forum for discussion and decision making in the care of lung cancer patients.

Targeted therapies

The role of targeted therapies, especially in NSCLC, is growing rapidly. At the moment, especially in adenocarcinoma, we can detect a so-called driving mutation in ~50% of the tumours. Unlike traditional chemotherapeutics, which interfere with cell division in all rapidly dividing cells, targeted therapies attempt to inhibit cell activity more selectively at the level of growth factor receptors and intracellular signalling cascades.

Epidermal growth factor receptor (EGFR) is involved in signalling cascades leading to cell division and proliferation. In tumour cells, mutations in and overexpression of the *EGFR* gene or downstream components of the EGFR pathway increase proliferation, survival and metastasis. Several targeted therapies attempt to interfere with this

Table 1. The major side-effects of chemotherapeutic agents

Nausea and vomiting	Cisplatin is highly emetogenic Prophylactic antiemetics should be given to all patients receiving chemotherapy Delayed nausea and vomiting may occur days after administration Commonly used antiemetics include dexamethasone, serotonin antagonists and neurokinin-1 inhibition
Neutropenia	Severe neutropenia refers to peripheral neutrophil counts $<500\ \text{cells}\cdot\mu\text{L}^{-1}$ Reverse isolation in hospitalised patients with severe neutropenia may reduce the risk of nosocomial infections Febrile neutropenia refers to elevated oral or axillary temperature (>38°C for >1 h or >38.2°C one-time measurement) in the setting of severe neutropenia, and should be treated with intravenous antibiotics The prophylactic use of granulocyte colony-stimulating factors can be considered in those at increased risk of developing febrile neutropenia
Anaemia	Consider transfusion in symptomatic patients or those with very low haemoglobin The use of erythrocyte-stimulating factors (*e.g.* erythropoietin) is generally not recommended; however, it can reduce the number of transfusions and improves fatigue
Neuropathy	Most commonly caused by the taxanes and vinorelbine
Fatigue	Multifactorial Malnutrition, anaemia and depression commonly play a role

abnormal EGFR activity: erlotinib and gefitinib, as well as afatinib and osimertinib, are tyrosine kinase inhibitors (TKIs) that inactivate the intracellular portion of EGFR, whereas cetuximab, as an antibody, binds to the extracellular domain of the receptor. All four EGFR TKIs are approved for the treatment of activating mutations. *EGFR* inhibitors do not cause typical chemotherapy side-effects, but commonly cause clinically significant rash, diarrhoea and liver enzyme elevation.

There is evidence that *EGFR* mutations in exon 19 and 21 (activating mutations) predict a good response to EGFR TKIs, whereas other mutations may cause resistance. A common resistance mutation is T790M, which can be treated by osimertinib. The classical *EGFR* mutations are associated with certain clinical characteristics (female patients, nonsmokers, adenocarcinoma and Asian ethnicity). First-line treatment with erlotinib has been demonstrated to improve progression-free survival in European patients harbouring *EGFR* mutation compared with first-line chemotherapy. In tumours with activating mutations, afatinib has shown an advantage regarding progression-free survival and for exon-19 mutation, as well as overall survival. In addition, erlotinib is approved as a second- or third-line therapy in NSCLC regardless

Table 2. Considerations for individual chemotherapeutic agents

Cisplatin	Highly emetogenic (appropriate use of antiemetics is essential) Nephrotoxic: avoid in patients with reduced GFR Pre-hydration (≥500 mL NaCl 0.9% per 50 mg cisplatin) reduces the risk of nephrotoxicity
Carboplatin	Consider as alternative to cisplatin in elderly patients or those with contraindications to cisplatin, dosed at AUC
Vinorelbine	May cause neuropathy or neutropenia Available in pill form for oral administration
Gemcitabine	30-min infusion time (more toxicity with slower infusion), avoid combination with radiotherapy due to increased side-effects
Pemetrexed	Short (10-min) infusion time Effective in patients with nonsquamous cell NSCLC and mesothelioma The risk of myelosuppression can be significantly reduced by vitamin B_{12} (1000 IU intramuscularly every 9 weeks) and folate (0.35–1 $mg \cdot day^{-1}$)
Paclitaxel	Premedication to prevent allergic reaction is required (dexamethasone and antihistamine)
Docetaxel	Premedication to prevent allergic reaction is required (dexamethasone)

GFR: glomerular filtration rate; AUC: area under the curve.

of *EGFR* mutation status. Afatinib is licensed for second-line treatment of squamous cell lung cancer without the existence of activating EGFR mutations.

Usually, a secondary resistance develops during treatment with erlotinib, gefitinib or afatinib, which is, among others, caused by *MET* amplification or resistance mutations in *EGFR*. In this situation, further treatment in clinical trials would be possible. In a large proportion of these tumours the resistance is caused by a T790M mutation.

Table 3. The World Health Organization/Eastern Cooperative Oncology Group scale

Performance status	Description
0	Patient is fully active and unrestricted in daily activities
1	Patient cannot carry out physically strenuous activities but is able to care for themselves and carry out light work
2	Patient is ambulatory and can care for themselves but is unable to work Up and about for >50% of waking hours
3	Patient is limited in self-care activities and confined to bed or chair for >50% of waking hours
4	Completely disabled Cannot care for self Totally confined to bed or chair

This mutation can be treated specifically with osimertinib. Osimertinib has also demonstrated clinical benefit in the first-line setting.

Further treatable growth-activating targets are *ALK* (anaplastic lymphoma kinase) gene rearrangements, which occur in ~3–5% of NSCLC, especially in adenocarcinoma. *EML4* (echinoderm microtubule-associated protein-like 4)–*ALK* fusion is especially found in patients with NSCLC. Crizotinib is a TKI of MET, c-Ros and ALK. Phase II data have shown these tumours to be highly sensitive to the ALK TKI crizotinib. Crizotinib is approved for the treatment of *EML4–ALK*-positive NSCLC and NSCLC with ROS1 fusions. There are further approvals for inhibition of EML4-ALK for ceritinib, alectinib and brigatinib. Further actionable mutations are *HER2* and *B-RAF V600E*.

Because tumours are dependent on the growth of new blood vessels, inhibition of angiogenesis is of major therapeutic interest. Bevacizumab is a monoclonal antibody against vascular endothelial growth factor. In stage IIIB and IV NSCLC patients, there is evidence that the addition of bevacizumab to platinum-based doublets is beneficial. The combination of bevacizumab with carboplatin plus paclitaxel was shown to provide a survival benefit, whereas the combination of bevacizumab with cisplatin plus gemcitabine only showed a benefit in progression-free survival.

Bevacizumab can cause severe haemoptysis, as seen in a randomised phase II trial, mostly in patients with squamous cell histology. Thereafter, most studies have excluded patients with brain metastases, previous haemoptysis, cavitary lung lesions or concurrent anticoagulation.

In second-line therapy, the anti-angiogenetic agents nintedanib (a TKI for adenocarcinoma) and ramucirumab (an antibody for NSCLC) demonstrated some benefit in combination with docetaxel.

Immune checkpoint inhibitors

Many previous immunotherapy approaches aiming to direct and strengthen the immune system's anti-tumour activity failed to show clinical benefit. Manipulation of the interaction between PD-1 and the ligand PDL-1 has been successful in multiple phase III trials in NSCLC and is under investigation in other thoracic tumours. Tumour cells can induce immune tolerance and block, among others, T-lymphocytes by producing and sending PD-L1, which binds to the corresponding receptor on the T-lymphocytes hereby blocking the activity of T-lymphocytes. If this action is blocked by an antibody against the PD-L1 receptor (nivolumab or pembrolizumab) on the T-lymphocyte or against the ligand PD-L1 (atezolizumab or durvalumab), the original activity of the T-lymphocyte can be restored and tumour cells can be destroyed. The presence of PD-L1 alone is not sufficient and there are other not yet fully understood mechanisms involved. Among others there probably has to be enough tumour antigen expression to get an adequate immune response. Checkpoint inhibition does not cause the typical side-effects of chemotherapy. Its most relevant side-effects are autoimmune diseases caused by the increased T-lymphocyte activity. While generally manageable through discontinuation of checkpoint inhibition and use of immune suppression, autoimmune side-effects can be severe and, rarely, fatal. The awareness of these side-effects has to be present and corresponding guidelines have to be followed.

A further immune checkpoint, which can be re-activated, is CTLA-4. This immune checkpoint inhibitor is located earlier in the cycle of immune response. CTLA-4 antibodies help to improve the priming and invasion of T-lymphocytes in the tumour. CTLA4-antibodies were first applied in melanoma, with good success.

Following the success of checkpoint inhibition in melanoma, PD1 and PDL-1 inhibitors were investigated in NSCLC. Nivolumab demonstrated an overall survival benefit and a better side-effect profile in comparison to docetaxel in recurrent squamous and nonsquamous NSCLC. Pembrolizumab was studied in PD-L1 expressing tumours and showed similar benefits under these circumstances. Atezolizumab demonstrated a similar efficacy. All three drugs are licensed for recurrent disease.

First-line pembrolizumab in comparison to chemotherapy was effective in tumours with high PD-L1 expression as monotherapy and is licensed in this setting. There are several large randomised trials which successfully added PD1/PD-L1 inhibition to chemotherapy. This is also true for the combination of CTLA-4 inhibition (ipilimumab) and PD1 inhibition in tumours with a high mutational burden.

Small cell lung cancer

First-line therapy

Small cell lung cancer (SCLC) is almost always a systemic disease and, in most cases, the initial response to chemotherapy is quite good.

Cisplatin plus etoposide is a frequently used first-line combination, although carboplatin can be used instead of cisplatin in patients with poor prognosis/performance status or contraindications to cisplatin. Another commonly used but less effective regimen is adriamycin, cyclophosphamide and vincristine. In SCLC, chemotherapy offers a clear survival benefit, from 4–6-week survival in untreated patients with extensive disease, to 12-month survival in extensive disease with chemotherapy. The addition of atezolizumab during chemotherapy and afterwards as maintenance therapy led to a slightly improved progression-free and overall survival.

Second-line therapy

The second-line treatment of SCLC has been shown to increase survival and quality of life compared with best supportive care alone. Here, the choice of medications depends on the length of time since the initial response. For patients whose tumours initially respond well to chemotherapy and then go on to recur or progress >3–6 months later, the medications used in first-line treatment can be given again. Tumours that progress <3 months after the end of first-line therapy should be treated with different agents: in this setting, topotecan monotherapy is a common choice and can be given intravenously or orally. If the tumour does not respond to first-line therapies or progresses quickly after chemotherapy, second-line treatment is usually recommended. Inclusion in clinical trials or best supportive care alone are also reasonable options. There are clinical trials among others with immune checkpoint inhibitors and TLR9 agonists, a new cytotoxic agent and an antibody conjugate of the Notch pathway.

Multimodal therapy

Studies have shown that adjuvant chemotherapy improves survival in SCLC patients with completely resected, very limited disease. In patients with limited disease, local radiation is generally combined with chemotherapy. Concurrent chemoradiation regimens including cisplatin are the most effective. In extensive SCLC, thoracic radiation may be considered in patients who have responded well to chemotherapy.

Prophylactic cranial irradiation has been shown to improve survival in SCLC patients who reach a good remission after chemotherapy, including those with extensive disease at the time of diagnosis. One randomised Japanese trial demonstrated the option of omitting prophylactic cranial irradiation in case of regular frequent MRI examinations.

NSCLC

In stage II NSCLC adjuvant chemotherapy mostly cisplatin and vinorelbine is usually given.

In operable stage III NSCLC, neoadjuvant as well as adjuvant chemotherapy provide a survival benefit of ~5%.

In inoperable stage III NSCLC, simultaneous chemoradiotherapy (two cycles of cisplatin and vinorelbine, pemetrexed or etoposide) is the standard of care and can be complemented by maintenance therapy with durvalumab in patients who have at least stable disease and whose tumours express PD-L1.

In stage IV NSCLC we discriminate between tumours harbouring driver mutations, tumours with a high expression of PD-L1 and tumours without driver mutations and no high expression of PD-L1. These markers have to be evaluated.

First-line treatment with targeted therapies (see above) is an option for patients with specific mutations. This is especially true for activating EGFR mutations and EML4–ALK fusions, as well as ROS1 fusions and B-RAF V600e mutations.

If the tumour is expressing a high proportion of PD-L1 (>50%) monotherapy with pembrolizumab can be given. This leads to less toxicity, but it is not clear in advance, who will benefit or who will even belong to the hyperprogressors.

Chemotherapy is the treatment of choice for most NSCLC patients with metastases or malignant pleural effusion, although its efficacy is limited. In fit patients, first-line treatment should consist of cisplatin (or carboplatin) paired with one of gemcitabine, docetaxel, paclitaxel, pemetrexed or vinorelbine, administered over four to six cycles. The increase in survival offered by platinum-based chemotherapy is in the range of several months, although some patients experience durable responses, and there is evidence that chemotherapy improves patients' quality of life and performance status. Unfortunately, ~40% of NSCLC tumours do not respond to chemotherapy and only 20% of NSCLC patients experience significant regression of their tumours. In earlier randomised trials with platinum-based chemotherapy doublets (cisplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/docetaxel, vinorelbine/cisplatin or carboplatin/paclitaxel), there were no significant differences in response rate or overall survival. More recent studies show that histology plays a role in the response of NSCLC to various chemotherapeutic medications. In particular, nonsquamous histology (adenocarcinomas and large cell NSCLC) is predictive for better activity of pemetrexed.

In patients without driver mutations the addition of pembrolizumab to pemetrexed and cis-/ carboplatin in nonsquamous and to paclitaxel or nab-paclitaxel in squamous NSCLC followed by pembrolizumab maintenance therapy is licensed in Europe. Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin is licensed for nonsquamous NSCLC.

Patients with poor performance status may not tolerate platinum-based doublet chemotherapy but can often be treated with a single chemotherapeutic agent, for instance gemcitabine or paclitaxel, or in some cases with a carboplatin-based doublet. Specific mutations and the expression of PD-L1 should be evaluated.

Second-/third-line therapy

Second-/third-line chemotherapy in NSCLC generally involves monotherapy with a chemotherapeutic agent (docetaxel for all NSCLC histologies and pemetrexed for nonsquamous histology) or treatment with a PDL-1 or PD-1 antibody. If the recurrence is not early or rapid, treatment with PD1-/PD-L1-inhibitors is usually preferred. Docetaxel may be combined with ramucirumab or, in patients with adenocarcinoma, with nintedanib. This is probably especially indicated in early or rapid progressing tumours. An additional second- or third-line option for patients with wild-type EGFR is the use of the EGFR TKIs erlotinib and afatinib. Participation in phase II or III clinical trials with newer targeted agents may offer patients the option of treatment with medications not yet available on the market. There is some recent evidence that early second-line or maintenance therapy with an alternative medication (switch maintenance) or with one of the original substances (continuation maintenance) may be beneficial, perhaps especially for patients who did not respond particularly well to first-line chemotherapy (stable disease patients compared to partial/complete responders).

If nonsquamous tumours with EGFR mutations or EML4–ALK fusions are already treated with the specific TKIs they can get atezolizumab in combination with bevacizumab, paclitaxel and carboplatin.

Malignant mesothelioma

If systemic treatment is applied, usually cisplatin plus pemetrexed is given. The data in the literature are not adequately elaborated; in practice, more than six cycles are often used. In patients with contraindications to cisplatin, the off-label use of carboplatin can be considered. In a French randomised trial the addition of bevacizumab was of benefit. There is evidence supporting off-label second-line treatment with vinorelbine, gemcitabine or, in some cases, pemetrexed. Many trials are using or adding immune checkpoint inhibitors (PD-1/PD-L1-inhibitors ± CTLA4 inhibitors) to the treatment regimens.

Palliative treatments

In advanced lung cancer, progressive tumour growth in the central airways can produce haemoptysis, cough and airway obstruction leading to shortness of breath or pneumonia. In these situations, quality of life may primarily be improved through the palliative use of endoscopic tumour debulking techniques or prosthetic measures. Brachytherapy is also an effective option for the local treatment of tumour growth in or around the central airways, and stents may be used to maintain airway patency in patients with compression due to tumour. General supportive/palliative measures and psycho-oncology are applied additionally as needed.

Palliative radiation provides symptomatic relief in patients with brain and bone metastases. Pleurodesis and indwelling tunnelled catheters are an option for patients with recurrent malignant pleural effusions.

Further reading

- Baas P, *et al.* (2015). Malignant pleural mesothelioma: ESMO clinical practice guidelines. *Ann Oncol*; 26: Suppl. 5, v31–v39.
- Bohlius J, *et al.* (2019). Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update. *J Clin Oncol*; 37: 1336–1351.
- Brahmer JR, *et al.* (2018). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*; 36: 1714–1768.
- Früh M, *et al.* (2013). Small-cell lung cancer: ESMO clinical practice guidelines. *Ann Oncol*; 24: Suppl. 6, vi99–vi105.

- Hanna N, *et al.* (2017). Systemic therapy for stage IV non–small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*; 35: 3484–3515.
- Kalemkerian GP, *et al.* (2017). Molecular testing guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors: American Society of Clinical Oncology endorsement of the college of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology clinical practice guideline update. *J Clin Oncol*; 36: 911–919.
- Kindler HL, *et al.* (2017). Treatment of malignant pleural mesothelioma: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*; 36: 1343–1373.
- Novello S, *et al.* (2016). Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines. *Ann Oncol*; 27: Suppl. 5, v1–v27.
- Planchard D, *et al.* (2018). Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*; 29: Suppl. 4, iv192–iv237.
- Roila F, *et al.* (2016). 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. *Ann Oncol*; 27: Suppl. 5, v119–v33.
- Scherpereel A, *et al.* (2010). Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. *Eur Respir J*; 35: 479–495.
- Spiro SG, *et al.*, eds. (2009). Thoracic Malignancies. European Respiratory Monograph. Sheffield, European Respiratory Society.
- Taplitz RA, *et al.* (2018). Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update summary. *J Clin Oncol*; 14: 250–255.

Surgical treatment for lung cancer

Gilbert Massard, Anne Olland and Pierre-Emmanuel Falcoz

Despite the considerable progress made in thoracic oncology over the past 30 years, surgical treatment based on anatomical resection with complete mediastinal lymph node dissection remains the mainstay of cure for nonsmall cell lung cancer (NSCLC). Although combined modality treatments based on neoadjuvant or adjuvant chemotherapy are credited with a slight advantage in survival, the area under the survival curve proves that the most substantial part of cure is owed to surgery. Further, regardless the stage, survival after surgery is consistently longer than following alternative oncologic treatments.

Contemporary alternatives to surgery for small tumours are stereotaxic radiotherapy and radiofrequency ablation (RFA); these treatments are not yet scientifically validated and ignore lymphatic spread. Although no randomised trial is available, where RFA and stereotaxic radiation therapy are compared, a critical review of published papers led to the conclusion that the complication rate and recurrence rate are higher after RFA. The American National Cancer Database offered a large sample to compare outcomes after surgery and stereotaxic radiation therapy in stage 1 patients. Rough survival and disease-free survival were longer in surgical patients, matched to radiation therapy patients who were considered operable but who declined surgery.

In the N2 category, surgery has been challenged by exclusive radiochemotherapy in two stand-alone trials. The EORTC trial published in 2007 showed no difference between the two arms, but was flawed due to an incomplete resection rate of nearly 50%. The trial carried out by Albain *et al.* (2009) showed a 4% difference in favour of

Key points

The following recommendations are evidence based.

- Optimal results are obtained by specialised surgeons working in high-volume units.
- Anatomical resection combined with a complete lymph node dissection is the gold standard. Increasingly, video-assisted thoracoscopic surgery (VATS) is becoming an alternative to open surgery in patients with small tumours.
- Bronchoplastic and angioplastic lobectomies are viable alternatives to pneumonectomy, provided that a complete resection can be achieved.
- Segmentectomies could be applied to high-risk patients with tumours <2 cm in diameter; wedge excisions may be recommended for very small lepidic (former bronchoalveolar) adenocarcinoma (ground-glass opacity).

surgery, overall this was not considered significant; however, there was a significant survival advantage when resection was limited to lobectomy. It is unclear whether neoadjuvant therapies are more beneficial to the N2 population or to those with incipient disease. Meta-analysis demonstrated a benefit for patients undergoing adjuvant therapy; this is of weak clinical relevance for the individual patient, given that treatment of 20 patients is needed to save one at 2 years. The result deteriorates in the long term, and long-term complications of chemotherapy appear in survivors. In summary, the optimal treatment in operable patients remains radical surgery complying with oncologic principles. The classic approach of open thoracotomy is increasingly substituted with VATS for small tumours. Generalisation of screening programmes with low-dose CT is expected to increase considerably accrual of small, T1 tumours in the future (National Lung Screening Trial Research Team, 2011).

Work-up of the patient should include a fitness check-up according to the European Respiratory Society (ERS)/European Society of Thoracic Surgeons (ESTS) guidelines.

The aim of this chapter is to describe the quality requirements of contemporary oncologic thoracic surgery, based on recommendations issued by a working group of the French Society for Thoracic and Cardiovascular Surgery.

How can we define early-stage lung cancer?

There is no universal definition of early-stage lung cancer. It seems adequate to restrict this label to patients with reasonable chances of survival. Since lymph node invasion at the N2 level is a marker of poor prognosis, the medical oncologist would certainly restrict the definition to stages N0 and N1.

For the surgeon, the survival advantage appears when the disease is accessible to a complete resection. Minimal N2, defined as microscopic metastasis to a single N2 node, is credited with a survival rate of 30–35% at 5 years, which is comparable to the worst N1. Furthermore, resectable T4N0 disease, such as selected cases of Pancoast tumours or main carinal invasion, may achieve a 5-year survival of >40%.

Individual cases should be discussed in a multidisciplinary tumour board with mandatory presence of a qualified thoracic surgeon. Any decision to decline an operation must be validated by a qualified thoracic surgeon.

What are the usual survival figures?

The following figures drawn from the classic surgical literature apply to surgical treatment, regardless of any neoadjuvant or adjuvant treatment.

For stage I, the usual figures (5-year survival) vary from 55% to 75% with a substantial difference between T1 and T2. Survival is further influenced by the type of resection (lobectomy *versus* pneumonectomy) and the comorbidity, which accounts for half of late deaths (table 1).

Table 1. 5-year survival following stage I disease: independent factors of prognosis

	Yes %	No %	p-value	Relative risk
Pneumonectomy	53	62.7	0.031	1.55
Angio-invasion	54.5	61.9	0.029	1.85
Atherosclerosis	46.3	64.3	0.017	1.55

Data from Thomas *et al.* (2002).

Table 2. Comparison of 5-year survival for intralobar and extralobar N1

Study	**Patients n**	**5-year survival %**	
		Intralobar N1	**Extralobar N1**
Yano *et al*. (1994)	78	64	39
Van Velzen *et al*. (1997)	391	57	30
Riquet *et al*. (1997)	256	53	38

For stage II, reported 5-year survival rates vary between 35% and 50%. Besides a difference between T1N1 and T2N1, there is a very dissimilar survival pattern according to the intra- or extralobar location of the N1 node. Intralobar N1 is credited with 5-year survival close to 55%, whereas in extralobar N1 it reaches only 35% (table 2).

For stage IIIA-N2, survival rates at 5 years are considerably lower and range from 15% to 25%. However, minimal N2 is a subgroup with a possible survival rate of 35% at 5 years. There is a small subset of completely resectable IIIA-T4N0 disease (Pancoast tumours, main carina involvement) that can achieve a survival of close to 50% at 5 years. Importantly, these patients must be carefully selected after having been discussed in multidisciplinary meeting.

The large majority of patients with stage IIIB are inoperable and global survival at 5 years is <5%.

Quality requirements: the surgeon and the institution

Thoracic oncologic surgery is a specialised medical activity. Well-trained thoracic surgeons working in high-volume units obtain the best results.

Qualification of the individual surgeon

A comparison of the results of lung resections performed by either general or well-trained thoracic surgeons in a cohort of 1583 cases of resection for lung cancer performed between 1991 and 1995 showed that operative mortality was twice as high when resection was performed by general surgeons. It is remarkable that 75% of general surgeons performed <10 resections during the observation period.

Qualification of thoracic surgeons depends on the national rules in different European countries. In an attempt at harmonisation over the European territory, the European Union of Medical Specialists (UEMS) has created the European Board of Thoracic Surgery certification, which may be obtained by an examination conducted every year. Further, a task force set up by the ESTS and ERS has defined a European syllabus for thoracic surgery.

Hospital volume and its impact on post-operative mortality

A review of data from the Medicare registry between 1994 and 1999 revealed that operative mortality following lobectomy varied from 6.4% in a low-activity centre (fewer than nine cases per year) to 4.2% in a high-activity centre (>46 cases per year); following pneumonectomy, the range extended from 17% to 10.6%, respectively. A review of the French National database EPITHOR has defined a threshold of 35 operations per year per institution, where operative mortality decreases significantly.

We may conclude that a high hospital volume warrants the necessary routine not only of the operating surgeon, but also of the surrounding team.

Hospital volume and its impact on long-term survival

A study that included 2118 patients operated upon in one of 76 hospitals over a 10-year period, divided into quintiles according to hospital volume, confirmed that hospital volume affects not only early outcomes but also long-term survival. Operative mortality ranged from 3% at high-volume units to 6% at low-volume units; operative morbidity ranged 20–44%. The 5-year survival decreased from 44% at high- to 33% at low-volume centres.

Basic principles of surgical treatment: complete anatomic resection and complete lymph node dissection

The basic principles described here are based on recommendations issued by a working group of the French Society for Thoracic and Cardiovascular Surgery. A complete cancer operation requires anatomic resection of the primary lesion and complete homolateral lymph node dissection.

Complete anatomic resection

Anatomic resection means either lobectomy or pneumonectomy with precise hilar dissection, according to the locoregional extent of the tumour. The rule is to privilege lobectomy whenever it enables a complete resection. Standard lobectomy is not possible if the tumour extends across the fissure, invades the main pulmonary artery or involves the bronchial tree proximal to the lobar take-off; a double location in different lobes is also an indication for pneumonectomy.

Lobectomy is preferred to pneumonectomy because of a substantially lower operative risk. Operative mortality is ~2% following lobectomy, and ranges from 6% to 10% following pneumonectomy. Mortality after pneumonectomy may be >10% in patients aged >70 years, or in case of extended resection. There is an ongoing debate whether mortality of pneumonectomy is increased after induction chemotherapy, especially on the right side. We have demonstrated a similar risk when compared to standard operations, confirmed by a French EPITHOR registry study; we observed a survival advantage even if the patient remained stage N2 after induction. Other disadvantages of pneumonectomy are decreased quality of life owing to loss of respiratory function and decreased possibilities of repeated curative resection should a metachronous primary cancer occur (~10% of stages I and II).

While lobectomy is considered as the gold standard, lesser resections may be justified for small tumours. Studies from Japan have shown the interest of parenchyma saving with segmentectomies for tumours <2 cm in diameter. A meta-analysis by Bao *et al.* (2014) has demonstrated a similar survival between lobectomy and segmentectomy for tumours <2 cm, whereas in all other scenarios lobectomy offers better chances for rough survival and disease-free survival.

When the tumour is invading surrounding anatomical structures, an enlarged *en bloc* R-0 resection may achieve satisfactory long-term results; this should be carried out in specialised institutions so that an excessive operative mortality does not erase the survival benefit of resection.

Complete homolateral lymph node dissection

The goals of lymph node dissection are:

1) To ascertain staging
2) To ensure complete resection of the disease

Staging is important at the individual level to set prognosis and to define the most appropriate treatment strategy. At the collective level, adequate staging facilitates comparison of different treatment modalities or results from different institutions.

Leaving unrecognised lymph node metastases obviously leads to ‘local recurrence’. CT underestimates N2 stage in one patient out of five and overestimates in one patient out of two. A negative positron emission tomography (PET) scan matches with mediastinoscopy or endobronchial ultrasound (EBUS) findings, but the latter are subject to a 10% failure rate. A positive PET requires histological assessment because the false-positive rate may reach 40%. Furthermore, >30% of patients with N2 disease have no apparent disease at the N1 level (so-called skip metastases). Even among patients with cT1 disease, 15–20% show mediastinal lymph node involvement.

As such, intraoperative exploration of the mediastinum is mandatory and can be achieved by two different procedures:

- Random sampling of nodes
- Complete node dissection

Obviously, only complete dissection appears to be serious and reliable. Importantly, in lung cancer surgery, there is no sentinel lymph node. The arguments for complete dissections are as follows.

In patients with pathological stage I-N0 disease, survival increases with the number of dissected nodes. This demonstrates that the more lymph nodes are harvested, the lower the risk of ignoring an invaded node and the more reliable the staging.

In a cross-sectional analysis, we compared sampling and dissection in each single case of 248 resections. Sampling identified 52% of resections as N2; multilevel N2 was identified in 42% of events only. Resection based on sampling alone would have been complete in only 12%.

The standard lymph node dissection is defined as an *en bloc* dissection with radical clearance of all lymphatic tissue areas long their anatomical borders (tracheobronchial tree, sheets of major vessels and oesophagus). On the right side, it includes lower oesophageal nodes within the pulmonary ligament, subcarinal space and paratracheal space. On the left side, it includes the pulmonary ligament, subcarinal space, aortopulmonary window, phrenic nodes and subaortic nodes up to the left tracheobronchial angle.

Formal lymph node dissection does not increase the post-operative complication rate. There is increasing evidence for a positive effect on survival. An initial nonrandomised study compared sampling to dissection in stage II and III, and concluded that there is a survival advantage following dissection. A randomised study including >500 patients demonstrated a survival advantage of node dissection without relation to a stage migration effect: it was observed not only stage-by-stage but also when comparing the two investigated groups as a whole (table 3). A meta-analysis concluded that 4-year survival was increased in patients having undergone node dissection, with a hazard ratio of 0.78.

Are there alternatives to pneumonectomy?

Given the high operative mortality rate of pneumonectomy, it is meaningful to look for alternatives. Bronchoplastic operations (sleeve lobectomy) are indicated:

1) when the tumour involves the lobar take-off on the endobronchial side; and
2) when positive N1 nodes with capsular disruption are identified at the origin of the lobar bronchus.

Table 3. Lymph node dissection increases survival: results of a randomised study

	5-year survival %	
	268 dissections	**264 samplings**
Stage I	82.2	57.5
Stage II	50.4	34.0
Stage III	27.0	6.2
Global	48.4	36.9

Reproduced from Wu *et al.* (2002), with permission from the publisher.

Angioplastic lobectomies are indicated when the lobar branches destined for the upper lobe cannot be divided safely with tumour-free margins; this situation is much more frequent on the left side for anatomical reasons.

The operative risk of bronchoplastic lobectomy is comparable to standard lobectomy, with a mortality of ≤2%. Long-term survival and rate of local recurrence match with reported data per stage (table 4). A meta-analysis showed that mortality was almost half that after pneumonectomy in experienced teams; 1-year survival was improved after bronchoplastic resection.

What is the impact of minimally invasive surgery?

Minimally invasive major resections, such as lobectomy and, more recently, segmentectomy, performed by VATS, are increasingly offered to patients with small tumours. Segmentectomy is usually performed in cases of impaired pulmonary function or small (<2 cm) peripheral lesions (Suzuki *et al.*, 2019). The common end-points are that, while operative mortality is similar to that of open procedures, there is a significant decrease in complication rates and length of hospital stay. Post-operative pain is considerably lower, recovery is faster and the social cost is decreased. As such, it may appear unethical to perform a thoracotomy in patients eligible for VATS, which is now considered the standard approach for the cT1N0 category (Falcoz *et al.*, 2014, Tsukazan *et al.*, 2018 and Zhao *et al.*, 2019). Robotic assistance offers a similar outcome to VATS, but with an increased cost due to sophisticated equipment and disposables; in addition, access to a robot is limited in most institutions.

Oncologic concerns may be addressed as follows. Minimally invasive resection can be recommended for T1 and small T2 tumours, and achieves equivalent long-term survival rates when compared with open surgery. Evidence for N1 or N2 disease

Table 4. 5-year survival following bronchoplastic lobectomy

First author	Stage I	Stage II	Stage III
Tedder *et al*. (1992)	63	37	21
Mehran *et al*. (1994)	57	46	0
Van Schil *et al*. (1996)	62	31	31
Massard *et al*. (1999)	70	37	8
Icard *et al*. (1999)	60	30	27
Tronc *et al*. (2000)	63	48	8

Data are presented as %.

primarily orientates towards classic open surgery, except for very experienced teams. There is no doubt that a precise anatomical dissection of the hilar structures (artery, vein and bronchus) can be safely performed. A negative PET lowers the risk for mediastinal lymph node involvement; furthermore, small tumours show a shift towards less invasive histology (adenocarcinoma with lepidic growth in particular). Nevertheless, a careful evaluation of the mediastinum with lymph node dissection is still recommended.

The demand for minimally invasive surgery will certainly be increased if lung cancer screening programmes with low-dose CT are generalised.

Further reading

- Albain C, *et al*. (2009). Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet*; 374: 379–386.
- Allen MS, *et al*. (2006). Mortality and morbidity of major pulmonary resections in patients with early stage lung cancer: initial results of the randomized prospective ACOSOG Z0030 trial. *Ann Thorac Surg*; 81: 1013–1019.
- Bao F, *et al*. (2014). Segmentectomy or lobectomy for early stage lung cancer: a meta-analysis. *Eur J Cardiothorac Surg*; 46: 1–7.
- Bendixen M, *et al*. (2016). Post-operative pain and quality of life after lobectomy *via* VATS or anterolateral thoracotomy for early stage lung cancer. *Lancet Oncol*; 17: 836–844.
- Berghmans T, *et al*. (2005). Survival improvement in resectable non-small cell lung cancer with (neo)adjuvant chemotherapy: results of a meta-analysis of the literature. *Lung Cancer*; 49: 13–23.
- Brunelli A, *et al*. (2009). ERS/ESTS guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J*; 34: 17–41.
- Cerfolio RJ, *et al*. (2003). The role of FDG-PET scan in staging patients with nonsmall cell carcinoma. *Ann Thorac Surg*; 76: 861–866.
- Chen FF, *et al*. (2013). Video-assisted thoracoscopic surgery lobectomy *versus* open lobectomy in patients with clinical stage 1 non-small cell lung cancer: a meta-analysis. *Eur J Surg Oncol*; 39: 957–963.
- Falcoz PE, *et al*. (2014). The impact of hospital and surgeon volume on the 30-day mortality of lung cancer surgery: a nation-based reappraisal. *J Thorac Cardiovasc Surg*; 148: 841–848.
- Falcoz PE, *et al*. (2016). Video-assisted thoracoscopic surgery *versus* open lobectomy for primary non-small-cell lung cancer: a propensity-matched analysis of outcome from the European Society of Thoracic Surgeon database. *Eur J Cardiothorac Surg*; 49: 602–609.
- Garelli E, *et al*. (2016). Microscopic N2 disease exhibits a better prognosis in resected non-small cell lung cancer. *Eur J Cardiothorac Surg*; 50: 322–328.
- Icard P, *et al*. (1999). Survival and prognostic factors in patients undergoing parenchymal saving bronchoplastic operation for primary lung cancer: a series of 110 consecutive cases. *Eur J Cardiothorac Surg*; 15: 426–432.
- Mansour Z, *et al*. (2007). Induction chemotherapy does not increase the operative risk of pneumonectomy! *Eur J Cardiothorac Surg*; 31: 181–185.
- Martinod E, *et al*. (2002). Management of superior sulcus tumors: experience with 139 cases treated by surgical resection. *Ann Thorac Surg*; 73: 1534–1540.
- Massard G, *et al*. (1999). Local control of disease and survival following bronchoplastic lobectomy for non-small cell lung cancer. *Eur J Cardiothorac Surg*; 16: 276–282.

- Massard G, *et al*. (2018). A harmonized European training syllabus for thoracic surgery: report from the ESTS-ERS task force. *Eur J Cardiothorac Surg*; 54: 214–220.
- McElnay P, *et al*. (2015). Outcome of surgery *versus* radiotherapy after induction treatment in patients with N2 disease. Systematic review and meta-analysis of randomised trials. *Thorax*; 70: 764–768.
- Mehran RJ, *et al.* (1994). Survival related to nodal status after sleeve resection for lung cancer. *J Thorac Cardiovasc Surg*; 107: 576–582.
- National Lung Screening Trial Research Team, *et al*. (2011). Reduced lung cancer mortality with low-dose computed tomographic screening. *New Engl J Med*; 365: 395–409.
- Paul S, *et al*. (2010). Thoracoscopic lobectomy is associated with lower morbidity than open lobectomy: a propensity-matched analysis from the STS database. *J Thorac Cardiovasc Surg*; 139: 366–378.
- Renaud S, *et al*. (2013). Is radiofrequency ablation or stereotaxic ablative radiotherapy the best treatment for radically treatable primary lung cancer unfit for surgery? *Interact Cardiovasc Thorac Surg*; 16: 68–73.
- Riquet M, *et al*. (1997). Prognostic value of T and N in non small cell lung cancer three centimeters or less in diameter. *Eur J Cardiothorac Surg*; 11: 440–444.
- Rosen JE, *et al*. (2016). Lobectomy *versus* stereotactic body radiotherapy in healthy patients withstage I lung cancer. *J Thorac Cardiovasc Surg*; 152: 44–54.
- Rosen JE, *et al*. (2016). The natural history of operable non-small cell lung cancer in the national cancer database. *Ann Thorac Surg*; 101: 1850–1855.
- Suzuki K, *et al*. (2019). Comparison of pulmonary segmentectomy and lobectomy: Safety results of a randomized trial. *J Thorac Cardiovasc Surg*; in press [https://doi.org/10.1016/j.jtcvs.2019.03.090].
- Swanson SJ, *et al*. (2014). Comparing robot assisted thoracic surgical lobectomy with conventional video-assisted thoracic surgical lobectomy and wedge resection: results from a multihospital database. *J Thorac Cardiovasc Surg*; 147: 929–937.
- Tagaki H, *et al*. (2011). Alice in wonderland of mediastinal lymph nodes. *J Thorac Cardiovasc*; 142: 477–478.
- Taioli E, *et al*. (2013). Long term survival in video-assisted thoracoscopic lobectomy *vs* open surgery in lung cancer patients: a meta-analysis. *Eur J Cardiothorac Surg*; 44: 591–597.
- Tedder M, *et al.* (1992). Current morbidity, mortality, and survival after bronchoplastic procedures for malignancy. *Ann Thorac Surg*; 54: 387–391.
- Thomas P, *et al*. (2002). Stage I non-small cell lung cancer: a pragmatic approach to prognosis after complete resection. *Ann Thorac Surg*; 73: 1065–1070.
- Thomas PA, *et al*. (2015). Pneumonectomy for lung cancer: contemporary national early morbidity and mortality outcomes. *J Thorac Cardiovasc Surg*; 149: 73–82.
- Tronc F, *et al.* (2000). Long-term results of sleeve lobectomy for lung cancer. *Eur J Cardiothorac Surg*; 17: 550–556.
- Tsukazan MTR *et al*. (2018). Video-assisted thoracoscopic surgery yields better outcomes than thoracotomy for anatomical lung resection in Brazil: a propensity score-matching analysis using the Brazilian Society of Thoracic Surgery database. *Eur J Cardiothorac Surg*; 53: 983–998.
- Van Meerbeeck JP, *et al*. (2007). Randomized controlled trial of resection *versus* radiotherapy after induction chemotherapy in stage IIIA-N2 non-small cell lung cancer. *J Natl Cancer Instit*; 99: 442–450.
- Van Schil PE, *et al.* (1996). Long-term survival after bronchial sleeve resection: univariate and multivariate analyses. *Ann Thorac Surg*; 61: 1087–1091.

- Van Velzen E, *et al.* (1997). Lymph node type as a prognostic factor for survival in T2 N1 M0 non-small cell lung carcinoma. *Ann Thorac Surg*; 63: 1436–1440.
- Whitson BA, *et al*. (2008). Surgery for early-stage non-small cell lung cancer: a systematic review of the video-assisted thoracoscopic surgery versus thoracotomy approaches to lobectomy. *Ann Thorac Surg*; 86: 2008–2018.
- Wright G, *et al*. (2006). Surgery for non-small cell lung cancer: systematic review and meta-analysis of randomized trials. *Thorax*; 61: 597–603.
- Wu YL, *et al*. (2002). A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. *Lung Cancer*; 36: 1–6.
- Yang C-FJ, D'Amico TA (2012). Thoracoscopic segmentectomy for lung cancer. *Ann Thorac Surg*; 94: 668–681.
- Yano T, *et al.* (1994). Surgical results and prognostic factors of pathologic N1 disease in non-small-cell carcinoma of the lung. Significance of N1 level: lobar or hilar nodes. *J Thorac Cardiovasc Surg*; 107: 1398–1402.
- Zhao W, *et al*. (2019). Comparison of lymph node dissection and lymph node sampling for non-small cell lung cancers by video-assisted thoracoscopic surgery. *J Thorac Dis*; 11: 505–513.

Radiotherapy for lung cancer

Luigi Moretti and Paul Van Houtte

Radiotherapy remains a major player in the treatment of patients suffering from lung cancer: half of patients will receive radiotherapy at some point in their disease history, either for cure or palliation. While surgery remains the treatment of choice for early-stage disease, the new radiotherapeutic techniques are becoming more than a simple alternative. For locally advanced disease, radiotherapy is increasingly a multimodal approach requiring close cooperation between surgeons and medical oncologists to select the best approach for each individual patient.

During the last decade, major improvements have been made both in imaging procedures and in radiotherapy delivery; for example, positron emission tomography (PET)-CT is now a major component of radiotherapy planning, allowing the selection and delineation of targets while protecting vital organs and structures such as the lungs, spinal cord and heart. Radiotherapy equipment has also evolved, with the implementation of multileaf collimators, gating techniques and three-dimensional

Key points

- For early-stage non-small cell lung cancer (NSCLC) patients, surgery (lobectomy or an anatomical segmentectomy with lymph node dissection) remains the standard treatment, while stereotactic body radiation therapy (SBRT)/stereotactic ablative radiation is indicated for medically inoperable patients.
- In locally advanced NSCLC, definitive concurrent chemoradiotherapy is preferred while surgery is used for selected cases (with induction or adjuvant chemotherapy).
- Postoperative radiotherapy is recommended for patients with positive surgical margins/incomplete resection, T4 disease (except nodule in same lobe) and/or pN2 disease.
- For limited small cell lung cancer (SCLC), concurrent chemotherapy and early chest radiotherapy are recommended.
- Prophylactic cranial irradiation is indicated for all stages of SCLC after response to primary therapy.
- For oligometastatic disease, SBRT may be considered within a multimodal approach.
- Palliative radiotherapy may be used to treat pain, bleeding, superior vena cava syndrome, cord compression and brain metastases.

Table 1. Overall survival based on stage at presentation and treatment applied

Disease stage	Overall survival	Median survival	Treatment
NSCLC			
I–II (early)	53–80% at 5 years 68–77% at 5 years	20–60 months	Surgery SBRT
III (locally advanced)	09–16% at 5 years 15–22% at 3 years	13–17 months	Chemoradiation
SCLC			
Limited	20–30% at 5 years 30–40% at 3 years 50% at 1 year	18 months	Chemoradiation
Extensive	0–2% at 3 years 27–40% at 1 year	7–10 months	Chemotherapy

image guidance directly at the treatment machine. This has led to substantial improvement in local control, quality of life and survival (table 1).

Mechanisms of action

At the cellular level, the most important effects of radiation are linked to double-stranded breaks in nuclear DNA, either by direct ionisation or by indirect formation of free radicals, by water radiolysis, that subsequently interact with DNA. Radiation can also affect the processes of the cell cycle and alter cell growth. When unable to repair the damage, cells undergo several types of death, *i.e.* apoptosis or senescence, and are ultimately cleared by normal physiological mechanisms. Similarly, adverse effects of radiation are mainly the consequence of radiation damage to surrounding normal tissues that were not able to repair adequately.

Tumour radiobiology

Tumour radiobiology is complex, as response depends not only on dose but also on individual radiosensitivity, timing, total dose, fraction size and other agents given concurrently (*i.e.* chemotherapy). It allows the optimisation of a radiotherapy schedule and therapeutic ratio for individual patients in regards to maximising tumour control probability while minimising normal tissue complication probability.

The biological factors that influence the response of normal and neoplastic tissues to classical fractionated radiotherapy are repair, redistribution, repopulation, reoxygenation and intrinsic radiosensitivity (the ‘five Rs’ of radiotherapy). Those factors are not applying for very high biologic doses used in ablative radiotherapy techniques (stereotactic body radiation therapy (SBRT)).

Techniques of radiotherapy

- Classical external beam radiation using a three-dimensional conformal radiation (3D-CRT) or, preferably, an intensity-modulated radiotherapy (IMRT), either static or rotational
- SBRT or stereotactic ablative radiation (SAR or SABR), both for the primary lesion and metastatic sites
- Brachytherapy techniques for endobronchial disease *via* fibreoptic bronchoscopy
- For palliation, two-dimensional (now outdated) or preferably 3D-CRT may be used

Radiotherapy planning and doses

Non-small cell lung cancer: stage III

For radiotherapy, the prescribed dose depends on the target volumes and the goal of the treatment (exclusive, preoperative or palliation), while taking into account the presence of organs at risk in the region to be treated. There is a clear relationship between the total dose, the delivery time and the local tumour control.

For chest radiotherapy, the Radiation Therapy Oncology Group (RTOG) 73-01 randomised trial established 60 Gy in 6 weeks to be the reference but the results were still disappointing, with <10% survival at 5 years and poor local control. This was partially related to the tools available at that time both for the treatment and the staging procedure. The paradigm was to use elective nodal irradiation to control possible microscopic spread, leading to a large volume of irradiation and subsequently limiting the possibility of dose escalation. Subsequently, we have moved from elective mediastinal irradiation to an involved site-only approach, *i.e.* to treat only the area of known disease given the possibility of increasing the radiation dose. Failure in a nonirradiated lymph node area is a rare event.

Furthermore, we have seen a series of new technological developments (multileaf collimators, PET-CT, four-dimensional CT, *etc.*); cone-beam CT on the linear accelerators allow image-guided radiotherapy for daily radiation delivery, improving treatment accuracy, and intensity-modulated radiation is more conformal to the target volume. It is also possible to control tumour movement during breathing. This has opened the way to more aggressive local treatments by increasing, either physically or biologically, the total radiation dose, but this requires a high quality of all procedures, especially good imaging performed in the treatment position and PET-CT within 3 weeks of the radiotherapy. Meanwhile, adding chemotherapy to chest radiotherapy has led to better survival, especially the concurrent approach, with improved local control but also more acute toxicity.

Several phase I and II trials have shown the possibility of increasing the dose above the ‘magic’ figure of 60 Gy. This was tested in a large phase III trial conducted by the RTOG: trial 06–17 addressed two questions, the total dose and the place of cetuximab. Patients were randomised to a standard dose of radiotherapy (60 Gy in 30 daily fractions) or a high dose (74 Gy in 37 fractions) concurrently with weekly paclitaxel and carboplatin followed by two cycles of consolidation and to cetuximab or not. The 2-year survival rates were 58% for the standard dose and 45% for the high radiotherapy dose. The local failure rate was also higher in the experimental arm: 38.6% *versus* 30.7%, respectively, at 2 years. The toxicity rates were not different between the two dose groups. A subsequent analysis looked at the role of IMRT, as patients were stratified according to the radiotherapy technique: the planning target volume was larger for patients treated with IMRT compared to those treated with 3D-CRT but the outcomes remained similar between the two techniques. Less grade 3 pneumonitis, lower heart dose and less dose reduction for chemotherapy were observed for patients treated with IMRT. Cardiac toxicity is becoming a major concern,and decreasing the dose to the heart is now an important parameter to take into account in radiation therapy planning.

Currently, 60–66 Gy in 6–7 weeks is considered the standard radiation dose, to be combined with a platinum-based doublet including a third-generation drug (*i.e.* paclitaxel, pemetrexed or vinorelbine). The optimal sequence and the type of chemotherapy must still be defined: should an induction or adjuvant chemotherapy be added to the concurrent approach? One advantage of induction chemotherapy is possible tumour downsizing and time to plan the radiotherapy but it is important to avoid any delay between the cycles of chemotherapy and the start of radiotherapy to prevent any tumour regrowth.

In cases of a preoperative chemoradiotherapy, the radiation dose is often limited to 45–50 Gy. This is the preferred approach for superior sulcus tumours for operable patients.

Although it remains controversial, post-operative radiotherapy is often recommended after surgical resection in cases of positive mediastinal nodes (pN2), extracapsular extension, T4 disease (except for nodules in the same lobe) or incomplete resection/ positive surgical margins. If there is no residual disease, the recommended dose is between 50 and 55 Gy in 20–25 fractions. A boost up to 66 Gy may be delivered to the area of residual disease.

Proton therapy is progressively being introduced in stage III non-small cell lung cancer (NSCLC) treatment. Protons have many potential advantages over photon therapy, owing to their physical characteristics. In theory, protons should allow to obtain a better dose distribution compared to photons, regardless of the technique used, especially for the dose to the heart. It remains to be determined how much clinical benefit the newly available technique achieves for NSCLC patients. The key issue is to see if a better dose distribution will indeed translate in a better outcome, and the answer will be provided by ongoing phase III trials.

Currently, there is no place for targeted agents or maintenance chemotherapy. Anti-PDL1 drugs are currently under investigation with promising early results.

Non-small cell lung cancer: stage II

SBRT or stereotactic ablative radiotherapy (SAR or SABR) is a novel form of high-precision, image-guided radiotherapy (table 2). The idea of SBRT is derived from the treatment of brain lesions by stereotactic radiosurgery, the intent of which is to ablate all malignant lesions with a very high radiation dose and achieve permanent local control, preferably in one session. SBRT extends the same concepts to small tumours within the body. Small lesions are most often defined as being <5 cm in maximum diameter. This treatment is only possible due to the development of highly advanced technologies that permit maximum dose delivery within the target while minimising the dose to the surrounding healthy tissue:

- accurate patient positioning
- breathing control
- motion control

Table 2. Comparison between SBRT and conventional fractionated 3D-CRT

SBRT	Conventional 3D-CRT
1–8 fractions	30–33 fractions
Short overall treatment time (convenience)	Long overall treatment time
High dose per fraction (>7.5 Gy)	1.8–2 Gy per fraction
High biological dose, ablative	Lower biological dose, normal tissue recovery
High-precision/advanced image targeting	Large fields/basic imaging
Steep dose gradients	Shallow dose gradients

- four-dimensional target definition
- use of multiple radiation beams
- reduction of the traditional margins linked to a more precise image-guided delivery

Ultimately, SBRT allows a very steep dose gradient compared to the shallow dose gradient obtained with standard fractionated radiotherapy. Typically, SBRT is given in one to eight high-dose (>5 Gy) fractions. This translates to delivering a very high biological effective dose ($\text{BED}_{2\,\text{Gy}}$>100 Gy).

Various machines may be used for SBRT, either linear accelerators with the adequate equipment or dedicated devices:

- Novalis Tx (Brainlab AG, Munich, Germany)
- Versa HD (Elekta Instrument AB, Stockholm, Sweden)
- Radionics XKnife (Integra, Plainsboro, NJ, USA)
- Axesse (Elekta Instrument AB)
- CyberKnife (Accuray Inc., Sunnyvale, CA, USA)
- TomoTherapy (Accuray Inc.)
- Gamma Knife (Elekta Instrument AB) (for brain only)

SBRT is commonly used to treat early-stage lung cancer in medically inoperable patients or those who refuse surgery, as well as metastatic sites (brain, bone, lung, *etc.*). For stage I NSCLC, this approach has changed the outcome of elderly patients with improved survival for treated patients compared to no treatment; this has been observed in various large-scale population databases.

Tumour location and size limit SBRT: currently, SBRT is mainly used for small tumours not close to the mediastinal structure as preliminary data have showed excessive toxicity when delivering high radiation doses to structures such as the main bronchial tree, the oesophagus and the heart (see figure 1 for location-dependent dose prescription in NSCLC). Two randomised trials including 100 patients have compared SBRT to a classical radiation schedule, showing the safety of the SBRT approach, which is more convenient for patients by reducing the number of sessions (<1 week *versus* 6–7 weeks). In this approach, only the tumour is irradiated without any coverage of the mediastinal lymph node. Only two small trials have compared surgery to SBRT for operable patients but due to the low number of patients, surgery should remain the first choice of treatment outside of clinical trials.

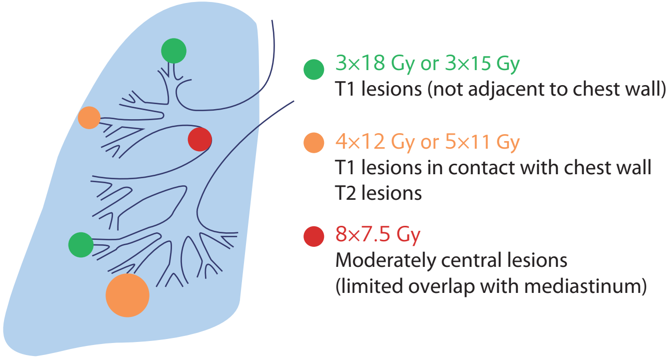

● 3×18 Gy or 3×15 Gy
T1 lesions (not adjacent to chest wall)
● 4×12 Gy or 5×11 Gy
T1 lesions in contact with chest wall
T2 lesions
● 8×7.5 Gy
Moderately central lesions
(limited overlap with mediastinum)

Figure 1. Risk-adapted lung SBRT dosing based on tumour location

Non-small cell lung cancer: stage IV

Another area of interest is to use SBRT to treat patients with an oligometastatic or oligoprogressive disease under targeted therapies and immunotherapies such as anti-PDL1 drugs. The former has become a highly controversial topic with treatment options ranging from conservative therapy to more aggressive modalities, with the principal aim to control the primary tumour and distant metastatic sites. There is a risk of overtreatment but two recent trials have showed a benefit in progression-free survival, while improved long-term survival was observed in retrospective studies. With anti-PDL1 drugs, an abscopal radiation effect has been described after the treatment of one location, and the regression of all the unirradiated metastatic sites and better survival. Many more trials are now ongoing. Clearly, the progress in systemic treatment has changed the outcome of patients with stage IV disease, outlining the importance of locally controlling the disease. This is well illustrated by the major improvement in survival for patients with brain metastases and *EGFR* mutation or *ALK* rearrangement.

Small cell lung cancer

The treatment of 'limited' disease includes early chest radiotherapy delivered concurrently with cisplatin/etoposide, preferably during the first two cycles. A recent phase III trial has compared the hyperfractionated schedule of 1.5 Gy twice daily for 3 weeks (total dose of 45 Gy) to 66 Gy in single daily fractions of 2 Gy (6.5 weeks) and no difference was observed in outcomes. Surprisingly, less oesophagitis was observed with the hyperfractionated schedule. It is advised to perform PET-CT for planning as it allows the avoidance of an elective mediastinal radiotherapy.

For 'extensive' disease, chemotherapy with cisplatin/etoposide remains the cornerstone of treatment. Chest radiotherapy may be considered after chemotherapy in cases of residual disease, to improve intrathoracic control.

Prophylactic cranial irradiation (PCI) should be given for all stages of small cell lung cancer in cases of a complete response to induction first-line treatment. The most accepted standard dose is 25 Gy in 10 fractions (2 weeks). It should be noted that there is currently no place for PCI in NSCLC outside of clinical trials. The data have shown a reduced rate of brain metastases but without any survival benefit. One concern is the risk of late sequelae, especially in terms of neurocognitive function. Studies are currently being conducted with the aim of sparing the hippocampus region, which plays an important role in the preservation of those functions.

Palliative radiotherapy

Radiotherapy may be used to relieve symptoms due to primary tumours or metastatic sites, such as pain, haemoptysis, dysphagia and dyspnoea. For primary lung tumours, various schedules are being used and proven adequate:

- 1×10 Gy, 2×8.5 Gy (with a 1-week interval)
- 5×4 Gy (daily)
- 10×3 Gy (daily)
- 13–15×3 Gy (daily)
- 20×2.5 Gy (daily)

The efficacy in terms of symptom relief is similar with all these schedules; the palliation response is more durable with higher radiation doses but at the price of more acute toxicity, especially oesophagitis. 10×3 Gy seems to be favoured among

Table 3. Radiotherapy main indications according to lung cancer stage

T1 N0 **T2 N0**	Surgery or SBRT
T3 N1 **T3 N2**	Multimodal approach including chemoradiation, chemotherapy and surgery
T3/T4 N3	Definitive chemoradiation
M1	Chemotherapy/targeted therapy/immunotherapy SBRT for oligo M1 or oligoprogressive M1 Radiotherapy for palliation if multiple M1

radiation oncologists, and has a good balance between palliation, 1-year survival and treatment time commitment.

For patients with good performance status and limited distant disease (*e.g.* oligometastatic), a definitive dose of radiation using SBRT or fractionated chemoradiation may be preferred in order to have sustained symptomatic improvement and continuing good performance status.

As always, the choice should take into account the needs of the patient, the tumour extent, the performance status and the specific symptoms (table 3).

Radiotherapy side-effects

Radiation-induced toxicity is related to the volume of normal tissues irradiated. The dose-limiting organs for chest radiation are the spinal cord, lung, oesophagus and heart. Classically, side-effects are divided into early/acute and late/chronic toxicity. These unwanted effects can be reduced using dose–volume constraints, which are modified by multiples factors, such as concurrent chemotherapy or surgery. Most of the toxicity data are derived from conventionally fractionated radiation and may not apply with SBRT, in which large doses per fraction are used. Although the results are not mature yet, several studies suggested limited early toxicity after SBRT for early-stage NSCLC not close to the central structures. Toxicities should be graded using the Common Terminology Criteria for Adverse Events system from the National Cancer Institute.

Common acute side-effects seen during radiotherapy for lung cancer include oesophagitis, skin irritation (dermatitis), cough, fatigue and nausea/vomiting. Most are resolved 2–4 weeks after radiotherapy. Acute pneumonitis can occur 1–6 months after radiation. Most patients have only radiographic changes without any clinical symptoms or functional end-point modifications. Clinical symptoms are cough, dyspnoea, hypoxia and fever. Symptomatic radiation pneumonitis can be treated with corticosteroids after excluding an infection.

Delayed complications include:

- pulmonary fibrosis
- pericarditis
- pericardial effusion
- coronary artery disease
- oesophageal stricture/fistula
- Lhermitte's syndrome
- brachial plexopathy

- rib fracture
- secondary cancers with a longer latency period

Pulmonary fibrosis usually evolves 6 months to several years after treatment. Several dosimetric parameters can be used to help predict the risk of pulmonary toxicity, commonly the V_{20} (the total lung volume receiving ≥20 Gy) and the mean lung dose (MLD). Current guidelines recommend a V_{20} below 30–35% and a MLD below 18–20 Gy. Additionally, the use of systemic chemotherapy may have a significant impact on toxicity and some drugs should be avoided in a concurrent approach, such as gemcitabine or bleomycin.

Globally, oesophageal toxicity is the most common acute toxicity during chest/mediastinal irradiation. While oesophagitis can be severe, it is rarely a reason to stop treatment if managed adequately. Dosimetric factors that influence oesophageal toxicity include the length of oesophagus receiving beyond 40–50 Gy and the mean oesophageal dose. Again, the use of concurrent chemotherapy with thoracic radiation significantly increases severe oesophagitis compared to radiation alone. Oesophageal stenosis or fistula remains a rare event using classical radiotherapy.

Since patients treated for locally advanced lung cancer typically have pre-existing cardiopulmonary disease, the risk of radiation-induced cardiovascular disease is rather difficult to define, but recent studies have outlined the occurrence of early cardiac problems. Therefore, the reduction of irradiated heart volume becomes an important issue in modern treatment planning of lung cancer to potentially reduce the risk of toxicity.

While rare and sometimes spectacular, Lhermitte’s syndrome (sudden electric shock-like sensations extending down the spine with head flexion) usually resolves spontaneously and is not predictive of chronic myelopathy. Spinal cord radiation injury is a very rare but serious complication of radiotherapy. Accordingly, most centres use conservative spinal cord dose constraints and limit the maximum dose to 45–50 Gy. Vertebral and rib fractures may also occur, especially in cases of osteoporosis or long-term corticosteroid treatment.

Caution should be used in treating central lesions with SBRT as they are at increased risk of toxicity compared to peripheral lesions. Central tumours are defined by the International Association for the Study of Lung Cancer as those located within 2 cm in all directions of any mediastinal critical structure, including the bronchial tree, oesophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve and recurrent laryngeal nerve. In addition, tumour volume is a significant predictor of severe toxicity, which suggests limiting the use of SBRT for early-stage NSCLC. Reported complications include pneumonitis, pleural effusion, haemoptysis and rib fracture, depending on initial tumour location. Accordingly, SBRT for apical lesions carries a risk of brachial plexus toxicity. Specific dose constraints are recommended for SBRT and risk-adapted dosing/schedules should be used for moderately central tumours. Clinical data with a longer follow-up are needed to better quantify the risk of late complications associated with SBRT.

Further reading

- Aupérin A, *et al*. (2010). Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol*; 28: 2181–2190.

- Bradley JD, *et al*. (2015). Standard-dose *versus* high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol*; 16: 187–99.
- Gomez DR, *et al*. (2016). Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol*; 17: 1672–1682.
- Graves PR, *et al*. (2010). Radiation pulmonary toxicity: from mechanisms to management. *Semin Radiat Oncol*; 20: 201–207.
- Guckenberger M, *et al*. (2016). Local tumor control probability modeling of primary and secondary lung tumors in stereotactic body radiotherapy. *Radiother Oncol*; 118: 485–91.
- Herskovic A, *et al*. (2017). Role of postoperative radiotherapy in pathologic stage IIIA (N2) non-small cell lung cancer in a prospective nationwide oncology outcomes database. *J Thorac Oncol*; 12: 302–313.
- Nanda R, *et al*. (2015). Stereotactic body radiation therapy versus no treatment for early stage non-small cell lung cancer in medically inoperable elderly patients: a national cancer database analysis. *Cancer*; 121:4222–30.
- Shaverdian N, *et al*. (2017). Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol*; 18: 895–903.
- Slotman BJ (2015). Should all patients with SCLC receive prophylactic cranial irradiation if they have responded to treatment? PCI should be offered in nearly all cases. *Clin Adv Hematol Oncol*; 13: 729–31.
- Van Houtte P, *et al*. (2017). Radiotherapy for locally advanced non-small cell lung cancer including combined modality. *In*: Pass H, *et al*., eds. *IASLC Thoracic Oncology*. 2nd Edn. Philadelphia, Elsevier; pp. 363–373.

Other lung tumours

Andrew Cheng and Matthew Evison

Pulmonary carcinoids

Pulmonary carcinoids are a rare type of malignant tumour accounting for 1–2% of all lung tumours. These well-differentiated neuroendocrine tumours are on the same spectrum of disease as poorly differentiated neuroendocrine tumours, such as high-grade large cell neuroendocrine tumours and small cell lung carcinoma. However, they express unique pathological characteristics and behaviours which lead to more favourable outcomes. Pulmonary carcinoid tumours fall into the World Health Organization (WHO) classifications of either low-grade typical carcinoids (TC) or intermediate-grade atypical carcinoids (AC), based predominantly on mitotic frequency and necrosis (table 1). The prevalence ratio between TC and AC is approximately 10:1.

Clinical features

Although well-differentiated neuroendocrine tumours can occur throughout the body, pulmonary carcinoids account for 25% of these tumours. They occur slightly more commonly in women with peak incidence in the fourth to fifth decades.

TCs often occur in never or light smokers, with an increased incidence of ACs in heavier smokers. There is also an association with multiple endocrine neoplasia type 1 (MEN-1), an autosomal dominant inherited disorder causing numerous neoplastic lesions of the endocrine system due to an absence or defect in the tumour suppressor, menin. In the MEN-1 cohort, pulmonary carcinoids have a prevalence of 5%.

Endobronchial lesions (up to 70% of pulmonary carcinoids) commonly result in haemoptysis, cough, recurrent chest infections and wheeze. However, peripheral tumours are generally associated with no symptoms and are commonly discovered incidentally.

Key points

- Pulmonary carcinoids are well-differentiated neuroendocrine tumours divided into low-grade typical carcinoids and intermediate-grade atypical carcinoids.
- Surgery remains the only curative treatment for pulmonary carcinoids, although systemic therapy may help with paraneoplastic syndromes.
- Benign tumours such as hamartomas and pneumocytomas are often incidental findings in asymptomatic patients.

Table 1. Histological classification of pulmonary carcinoids

	Typical carcinoid	Atypical carcinoid
Mitosis per 2 mm² (10HPF)	<2	≥2 and <10
Necrosis	Not present	Punctuate foci
Nucleoli	Small	Often prominent
Nuclear pleomorphism	Rare	Occasional
Proliferation index (Ki-67)	Low (<1%)	Intermediate (1–20%)
Histological grade	Low	Intermediate

HPF: high power fields. Ki-67 is a nuclear antigen expressed by proliferating cells.

Paraneoplastic syndromes

Similar to other neuroendocrine tumours, carcinoids contain neurosecretory granules that are capable of secreting hormones ectopically. Cushing's syndrome presents in 2–6% of pulmonary carcinoid patients. Ectopic hypersecretion of adrenocorticotropic hormone (ACTH) results in hypercortisolism. Of all the cases of ectopic ACTH secretion causing Cushing's syndrome, 40% are due to pulmonary carcinoid tumours. Manifestations include truncal obesity, moon facies, proximal muscle weakness, hypertension, glucose intolerance, hirsutism and hyperpigmentation.

Although rare (affecting 1–5% of pulmonary carcinoid patients), carcinoid syndrome can result from the hypersecretion of serotonin (5-hydroxytryptamine). Manifestations include flushing, diarrhoea, palpitations and wheeze. Carcinoid syndrome is far more common in gastrointestinal forms of carcinoid and is generally associated with metastatic disease in the liver. Carcinoid syndrome in pulmonary carcinoid tumours can, however, occur independently of liver metastases.

Uncommonly, pulmonary carcinoids are also able to secrete growth hormone-releasing hormone (GHRH), resulting in high levels of growth hormone and classical features of acromegaly.

Diagnosis

Chest radiography reveals well-defined rounded lesions in 40% of cases. Contrast CT imaging remains the gold standard. Central lesions are commonly described as well-defined round or ovoid structures with intense homogenous contrast enhancement due to high tumour vascularity. Peripheral lesions are commonly slow growing rounded solitary nodules. Unsurprisingly, nodal and distant metastases occur more often in ACs than TCs (nodal involvement of up to 70% compared with 5–20%).

Somatostatin receptor scintigraphy, also known as octreotide scanning, can be useful in addition to CT. Carcinoid tumours often overexpress somatostatin receptors on their cell surfaces and scintigraphic detection has a sensitivity of up to 80%.

Positron emission tomography (PET) with 2-fluoro-2-deoxy-ᴅ-glucose (FDG) shows low sensitivity in detecting low-grade TC tumours as they are often hypometabolic. A recent study of 207 surgically resected pulmonary carcinoid patients showed a sensitivity of only 33% with a specificity of 94% in diagnosing mediastinal lymph node disease. This contrasts with their poorly differentiated counterparts, where FDG-PET plays an important role. However, AC tumours often demonstrate significant FDG uptake.

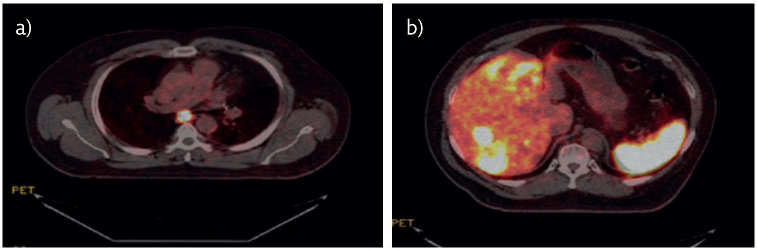


Figure 1. PET-CT with Gallium-68-labelled somatostatin analogue. Significant tracer uptake in a 60-year-old man with relapsed atypical carcinoid disease with liver metastases and lymphadenopathy a) above and b) below the diaphragm. Images courtesy of Was Mansoor (Medical Oncology, Christie Hospital, Manchester, UK).

Recently developed PET scanning with Gallium-68-labelled somatostatin analogues has shown superior sensitivity when compared with octreotide scanning and has played an important diagnostic role in centres which have access to this novel tracer (figure 1).

Bronchoscopy should be performed for centrally occurring lesions pre-operatively. Tumours typically have a highly vascular reddish appearance with a smooth surface covered with intact epithelium. Tissue biopsies for peripheral lesions are performed using percutaneous image-guided techniques.

Syndromic patients should undergo biochemical analysis. For those with Cushing's syndrome, measurements should include serum cortisol, 24-h urine free cortisol and serum ACTH. 5-hydroxyindoleacetic acid is the main metabolite of serotonin and can be tested in urine for carcinoid syndrome. Serum GHRH, growth hormone and insulin-like growth factor 1 should be tested in acromegaly.

Management

Surgical resection remains the gold standard of management and remains the only curative option. Surgery is guided by the location and staging of disease, and tissue type, along with the functional and physiological status of the patient.

Complete anatomical resection (lobectomy and nodal dissection) is recommended in peripheral carcinoids. Parenchymal-sparing surgery (such as bronchial sleeve resection) is favoured in central low-grade lesions. There is little evidence to guide metastatic resection, but this should be considered for patients with limited sites of spread as curative intent treatment.

Medical therapy is targeted at both tumour control and hormone hypersecretion. Systemic chemotherapy should be considered in those with inoperable advanced disease. However, conventional platinum-based regimes have shown disappointing results with limited effect and survival data. Single-agent temozolomide has demonstrated slight clinical benefit and has been used palliatively due to its safer toxicity profile. Peptide receptor radionuclide therapy on tumour somatostatin receptors with Lutetium-177 has shown a promising clinical response and survival data. More recently, molecular targeting with the mammalian target of rapamycin (mTOR) inhibitor everolimus has performed well in clinical trials (improvement in median progression free survival of 5.6 months) and has received widespread licensing.

Symptoms of hypersecreting tumours can be treated successfully with somatostatin analogues (SSA) such as octreotide or lanreotide, resulting in a symptomatic response rate of up to 60%. Ketoconazole is first line for ectopic ACTH secretion, which may also respond well to SSAs. Bilateral adrenalectomy is reserved as an option for refractory Cushing's syndrome. SSAs are also important for those undergoing surgical intervention in order to prevent carcinoid crisis caused by an overwhelming release of hormones from the tumour during manipulation.

Prognosis in TC is significantly better than AC, with 5-year survival of 87–100% in TC *versus* 40–59% in AC. Metastatic disease has a far poorer 5-year survival rate of 14–25%. Following surgical resection of early stage disease, 15% of typical pulmonary carcinoids and 50% of atypical pulmonary carcinoids relapse.

Hamartomas

Pulmonary hamartomas are the most common benign tumour of the lung, accounting for 3% of all lung tumours. Hamartomas were originally described as a congenital non-neoplastic malformation, but it is now considered a true benign mesenchymal tumour. They are composed of an abnormal mixture of cartilage (scattered with calcification), fat, smooth muscle, fibromyxoid connective tissue and occasionally bone.

Clinical features

Hamartomas are three times more common in males than females, with peak incidence in the sixth decade. The majority of patients are asymptomatic, with symptoms more common in endobronchial lesions.

Diagnosis

Diagnosis from imaging is often made incidentally. CT typically shows a peripheral solitary well-circumscribed rounded nodule with hypodense areas consistent with fat, dispersed with flakes of calcification. 95% of lesions are located within the lung periphery. The textbook description of 'popcorn-like' appearances are only evident in 10–30% of cases.

CT-only diagnosis has been described as accurate in 50–60% of cases. Tissue biopsy may be warranted for ambiguous cases by means of image-guided percutaneous lung biopsy, endobronchial radial ultrasound, or *via* flexible bronchoscopy.

Management

The vast majority of hamartomas are managed conservatively, usually following a period of interval imaging. Surgical resection is rarely indicated except for aggressively growing tumours and symptomatic patients.

Pneumocytomas

Pulmonary sclerosing pneumocytoma is a rare benign neoplastic tumour. Originally described by Liebow and Hubbell in 1956 as pulmonary sclerosing haemangioma, more recent immunohistochemical studies have shown that the tumour originates from the pulmonary epithelium (type II pneumocytes). Frequently they contain a macroscopic haemorrhagic component. In the 2015 WHO Classification of Lung Tumors, they are listed and renamed as sclerosing pneumocytomas under the category of 'adenoma'.

Clinical features

The peak incidence occurs in the fifth decade with a female preponderance of 5:1. As with other benign lung tumours, pneumocytomas often present in asymptomatic patients as an incidental finding.

Diagnosis

CT typically shows a solitary well-circumscribed rounded homogenous nodule. The presence of the haemorrhagic component leads to marked contrast uptake. Calcification is seen in a minority of cases. Studies have shown that 73% of tumours are <3 cm, but there are case reports of tumours up to 8 cm. FDG uptake is often found on PET-CT imaging with maximum standardised uptake values correlating with tumour size.

Management

Despite pneumocytomas being considered benign, their PET-CT behaviour can often lead to falsely positive interpretations of malignant disease leading to surgery. Perioperative frozen section may help with unnecessary lung resection, but fails to identify pneumocytoma in 25–56% of cases. Some authors have recommended resection and long-term follow-up due to the rare potential for malignant transformation with lymph node metastases, reported in ~4% of cases.

Further reading

- Caplin ME, *et al.* (2015). Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. *Ann Oncol*; 26: 1604–1020.
- Hage R, *et al.* (2003). Update in pulmonary carcinoid tumors: a review article. *Ann Surg Oncol*; 10: 697–704.
- Lim JH, *et al.* (2016). Pulmonary sclerosing pneumocytoma mimicking lung cancer: case report and review of the literature. *Thorac Cancer*; 7: 508–11.
- van den Bosch JM, *et al.* (1987). Mesenchymoma of the lung (so called hamartoma): a review of 154 parenchymal and endobronchial cases. *Thorax*; 42: 790–793.

Metastatic tumours

Elisabeth Quoix

The thorax is a common site of metastasis from various cancers, which may affect the pleura, pericardium, heart, lungs, hilar or mediastinal lymph nodes, bone (chest wall and vertebrae), and muscle. These metastases may induce mediastinal compression syndromes (Pancoast, superior vena cava syndrome, dysphagia, dysphonia, tamponade *etc.*), just like locoregional extension of a primary lung cancer.

Pleural metastases

These occur commonly in patients with haematological or solid tumours and they are responsible for significant symptoms (pain, cough and dyspnoea). Moreover, they generally recur at short intervals after thoracenteses, which therefore needs to be repeated or leads to placement of tunnelled pleural catheters or thoracoscopy with talcage. Lung cancer and breast cancer represent 50–65% of the causes of malignant effusions, followed by lymphomas, tumours of the genitourinary tract and gastrointestinal tract which account for 25% of the causes. However, an unknown primary is not a negligible cause of malignant pleural effusions (5–10%). Pathogenesis of the secondary malignant effusion is essentially due to tumour emboli to the visceral surface of the pleura with secondary seeding to the parietal pleura. Regarding lung cancer or breast cancer, direct tumour invasion is another possibility; whereas, for example, in lymphomas mediastinal lymphatic blockade is a potential cause. By contrast, not all pleural effusions observed during a malignancy are metastatic, but can be linked to pulmonary embolism, may be transudative secondary to atelectasis caused by lung cancer, or even be a complication of the treatment (post-operative chylothorax, post-radiation pleural effusion or due to some antimitotics). Comorbidities such as cardiac insufficiency may also be responsible.

Pericarditis

Tamponade due to pericarditis may be the first symptom of cancer. Pericarditis with effusion (figure 1) is far more frequently due to cancer than pericarditis without effusion during the first year following the diagnosis of a pericarditis (Søgaard *et al.*, 2017).

Key points

- The thorax is a common site of metastasis from several cancers.
- It is sometimes difficult to distinguish between primary lung cancer and metastases from other primaries.
- Prognosis is linked to the underlying primary.

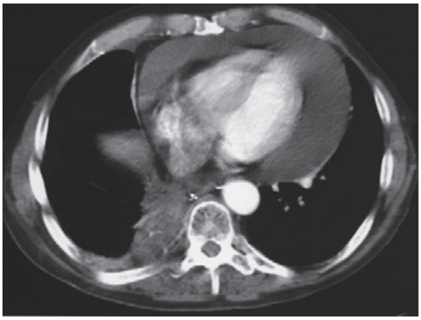


Figure 1. Pericardial effusion in a patient with right lower lobe carcinoma of the lung.

Overall, there were 1550 new diagnoses of cancer among 13 759 patients with acute pericarditis *versus* 1070 expected during a median follow-up of 6.4 years. During the first 3 months after pericarditis there are higher than expected rates of lung cancer, lymphomas and myeloid leukaemia. The main causes of pericarditis with pericardial effusion are lung cancer, lymphomas, breast cancer and leukaemia.

Pulmonary metastases

The lung is a prominent site of metastasis of breast, colon, kidney, uterus, and head and neck tumours. Some otherwise rare tumours (choriocarcinoma, osteosarcoma, testicular tumour, melanoma, Ewing tumour and thyroid carcinoma) frequently metastasise to the lung. Endothoracic metastases of breast cancer are essentially pleuropulmonary (figures 2a and b). In a review of 660 cases of breast cancers followed for a period of 5 years between 1975 and 1979, 119 endothoracic metastases were recorded. Among them, 79 were pleural or pleuroparietal, 80 were pulmonary (lymphangiitis, n=41; multiple nodules, n=34; solitary nodules, n=9; endobronchial, n=7; tumoural emboli, n=2; alveolar metastasis, n=1), 46 were hilar or mediastinal, and two were myocardial metastases (Kreisman *et al.*, 1983). Pulmonary metastases are also frequent in lung cancer and their prognosis appears to be of intermediate value if there is no other site involved; they are now classified as M1a since the seventh staging classification. Sometimes, pulmonary metastases may be excavated (figure 3) and may induce pneumothorax. Some may be calcified either spontaneously (osteosarcoma, giant cell tumour of the bone or papillary carcinoma of the thyroid) or after treatment.

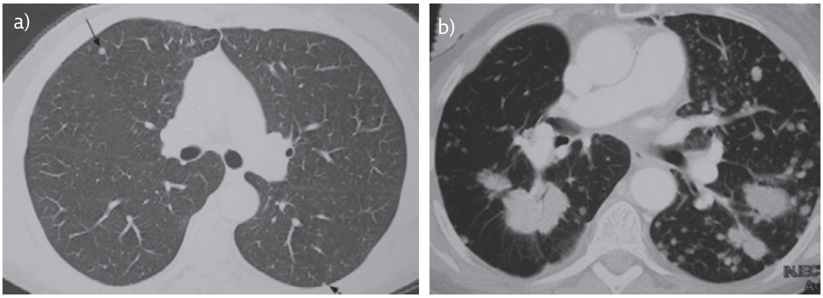


Figure 2. a) Multiple micronodules in a female who developed chronic cough 2 years after a breast cancer. b) The same patient 6 years later. Multiple secondary lesions of the lung are present, some of them displaying a pneumonic pattern.

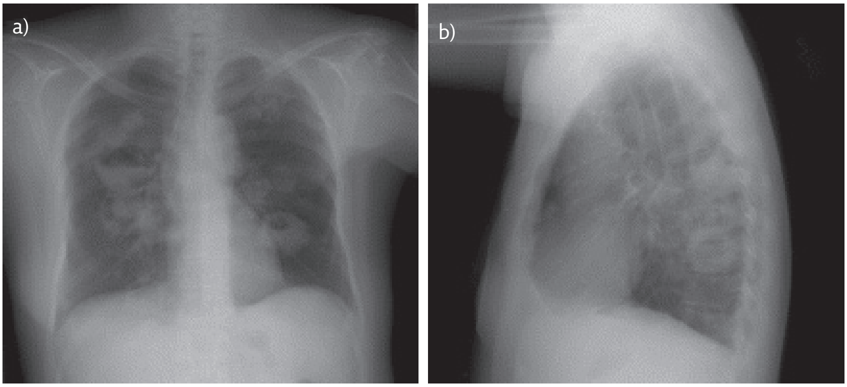


Figure 3. Multiple excavated pulmonary metastases from a head and neck carcinoma. a) Posteroanterior chest radiograph. b) Lateral chest radiograph.

Endobronchial metastasis is an infrequent feature (table 1). In a series of 174 cases endobronchial metastases from extrapulmonary primary, collected over a period of 18 years (representing 4% of the bronchial biopsies performed for cancer suspicion), 154 were metachronous and 11 synchronous. The latency between primary diagnosis and endobronchial metastasis was 136 months (range 0–300 months).

It may be quite difficult, if not impossible, to distinguish a primary lung cancer from endobronchial metastasis on a CT image. Endobronchial metastases from melanoma often appear black at endoscopy. Endobronchial metastases of a kidney cancer display strong enhancement on contrast-enhanced CT images. Whenever bronchofibroscopy is performed, there may be quite severe bleeding from the biopsy attempt; cough with haemoptysis is the most frequent symptom.

Tumoural emboli may have similar clinical and radiological features to thromboemboli; however, peripheral tumoural microemboli are characterised by normal imaging but respiratory failure (Chatkin *et al*., 2007). Diagnosis may be obtained by transbronchial biopsy or by videothoracoscopy; on histological examination, multiple carcinomatous emboli are visible in distal pulmonary arteries, veins and lymphatics.

Lymphangiitic carcinomatosis of the lung is observed with different primary sites, mainly the breast, stomach and pancreas. Clinically it is responsible for a dry cough, then progressive dyspnoea and thoracic pain. At the very beginning, the chest radiograph may be initially quite normal, then reticulomicronodulation appears

Table 1. Endobronchial metastases: frequency by primary site

Primary tumour site	Metastases n (%)
Breast	52 (30)
Colorectal	42 (24)
Kidney	24 (14)
Stomach	10 (6)
Melanoma	8 (4.5)
Prostate	8 (4.5)

Data from Marchioni *et al*. (2014).

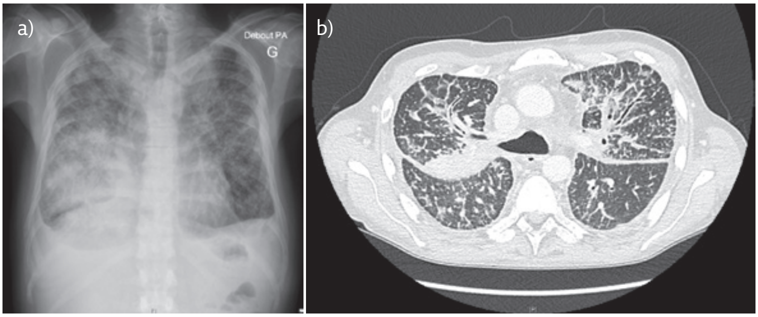


Figure 4. Advanced carcinomatous lymphangiitis of the lung. a) Advanced lymphangiitis in a 40-year-old man with adenocarcinoma of the right lower lobe. b) Small pleural effusion in the tissues and microreticular pattern typical of carcinomatous lymphangiitis.

predominating in the bases and may be associated with small pleural effusion, hilar and mediastinal lymph nodes (Figure 4).

Hilar and mediastinal metastatic lymph nodes

Metastatic hilar and mediastinal lymph nodes are mostly linked to an intrathoracic carcinoma. Among 565 patients, only 37 had a history of extrathoracic carcinoma in a surgical series (Riquet *et al.*, 2009). The primary cancer was most frequently breast, with others being from the kidney, testis, prostate, thyroid and other sites. Metastasis of breast cancer to intrathoracic nodes seems to occur quite frequently. In an autopsy series by Thomas *et al.* (1979) of women who had died of disseminated breast cancer, metastatic involvement of intrathoracic lymph nodes was found in 71% of cases. Lymph node involvement was more extensive in the mediastinum ipsilateral to the primary breast cancer than in the contralateral mediastinum.

Bone metastases in the chest

The bones of the chest are common sites of secondary lesions of lung, prostate and breast cancer, in which bone is the most common metastatic site.

Bone metastases affect 8% of patients with breast cancer. Bone scanning remains the mainstay for detection of bone metastases. In a meta-analysis of six studies comparing bone scanning and positron emission tomography (PET) without CT in breast cancer, a pooled lesion-based sensitivity of 88% and specificity of 87% was

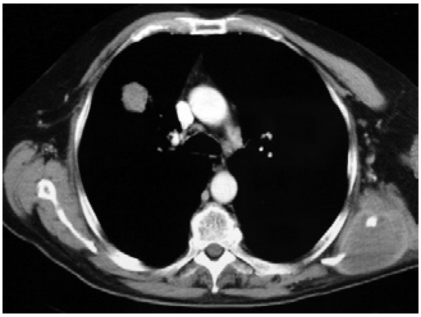


Figure 5. Left scapula osteolytic metastasis of a right upper lobe adenocarcinoma.

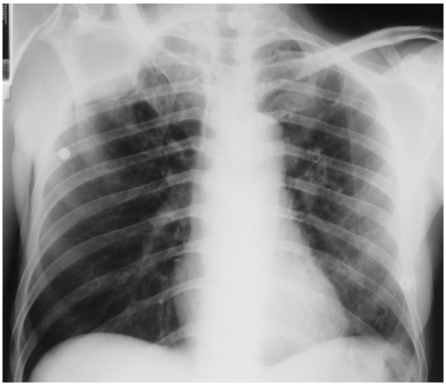


Figure 6. Osteolytic metastasis of the second right rib.

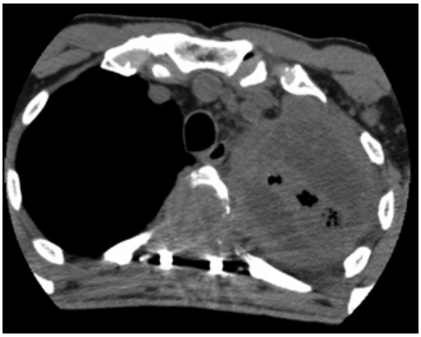


Figure 7. Vertebral metastasis responsible for spinal cord compression.

found for bone scanning, and a sensitivity of 69% and a specificity of 98% for PET (Shie *et al.*, 2008).

Bone is a frequent metastatic site in lung cancer (figure 5). In a recent study of 1000 patients, 105 (10.5%) had bone metastases at diagnosis (Song *et al.*, 2009). The sensitivity of PET/CT was 94.3% compared to 78.1% with bone scanning and the specificity was 98.8% and 97.4%, respectively. Among the 346 bone metastases detected by PET/CT, 55 were in the thoracic spine, 28 in the scapula or clavicles (figure 5), 12 in the sternum and 56 in the ribs (figure 6), *i.e.* 44% of the foci were in the chest. The main problem of PET is poor anatomical resolution.

MRI is the best imaging procedure whenever spinal cord compression is suspected. However, a CT-scan may be sufficient (figure 7).

Conclusion

The chest is a frequent site of metastasis, especially for lung, breast, kidney, prostate, colon and ovary carcinomas. The prognosis of these metastases is more related to the possibilities of control of the underlying neoplasm than to their possible immediate complications (*e.g.* tamponade). However, some metastases may alter quality of life, such as bone metastases, with a special attention to be paid to the spine because of the risk of spinal cord compression.

Further reading

- Chatkin JM, *et al.* (2007). Microscopic pulmonary neoplastic emboli: report of a case with respiratory failure but normal imaging. *Prim Care Respir*; 16: 115–117.
- Dizon DS, *et al.* (2008). The differential diagnosis of dyspnea in a woman with metastatic breast cancer–consideration beyond pulmonary embolism. *Breast J*; 14: 90–91.
- Kreisman H, *et al.* (1983). Breast cancer and thoracic metastases: review of 119 patients. *Thorax*; 38: 175–179.
- Marchioni A, *et al.* (2014). Endobronchial metastasis: an epidemiologic and clinicopathologic study of 174 consecutive cases. *Lung Cancer Amst Neth*; 84: 222–228.
- Riquet M, *et al.* (2009). Intrathoracic lymph node metastases from extrathoracic carcinoma: the place of surgery. *Ann Thorac Surg*; 88: 200–205.
- Shie P, *et al.* (2008). Meta-analysis: comparison of F-18 fluorodeoxyglucose-positron emission tomography and bone scintigraphy in the detection of bone metastases in patients with breast cancer. *Clin Nucl Med*; 33: 97–101.
- Song JW, *et al.* (2009). Efficacy comparison between 18-FDG PET/CT and bone scintigraphy in detecting bony metastases of non-small cell lung cancer. *Lung Cancer*; 65: 333–338.
- Søgaard KK, *et al.* (2017). Pericarditis as a marker of occult cancer and a prognostic factor for cancer mortality. *Circulation*; 136: 996–1006.
- Thomas JM, *et al.* (1979). The spread of breast cancer: importance of the intrathoracic lymphatic route and its relevance to treatment. *Br J Cancer*; 40: 540–547.

Pulmonary nodules

David R. Baldwin

Pulmonary nodules are a common finding on CT of the thorax (prevalence of 15–49%). Nodule prevalence is greater in screening trials and where the size threshold for reporting is lower. However, whether detected incidentally or through screening, nodules seem to have the same features that predict malignancy, so evidence from screening trials can be used to guide management of incidentally detected nodules. Management of pulmonary nodules is centred on prediction of the chance of malignancy and patient-informed decision making to reduce the chance of harm whilst accurately identifying and treating malignancy. The two most recent guidelines from the British Thoracic Society (BTS) and the Fleischner Society will be referenced throughout.

A pulmonary nodule is defined as a well or poorly circumscribed, approximately round structure appearing as a focal opacity on imaging that is ≤30 mm in maximum diameter. The vast majority of nodules are smaller than 10 mm, as detected on CT, and therefore much of the guideline recommendations apply to these. 'Solid' nodules obscure the underlying bronchovascular structures, whereas 'sub-solid' nodules have areas of ground-glass opacification that have greater attenuation than the lung, but the underlying bronchovascular structure is still visible. Sub-solid nodules (SSN) are further subdivided into pure ground-glass nodules (pGGN) (synonymous with 'non-solid' nodules) and part-solid nodules (PSN) where both solid and ground-glass components are seen (figure 1).

Initial assessment and criteria for discharge

Initial assessment focuses on determining which patients with nodules can be reassured and discharged, which require interval imaging and which need to be referred to the lung cancer team for further workup. Nodules that have benign pattern calcification ("popcorn") and those that have completely calcified are benign. Perifissural nodules are triangular or lentiform and closely associated with

Key points

- Pulmonary nodules may be classified into solid and sub-solid; the latter group are in turn divided into part-solid and pure ground-glass (also termed 'non-solid') nodules.
- Management of pulmonary nodules is centred on prediction of the chance of malignancy.
- Decisions on treatment depend on the risk of malignancy after further investigations, the growth characteristics where interval imaging is available, and on the fitness and preferences of the patient.

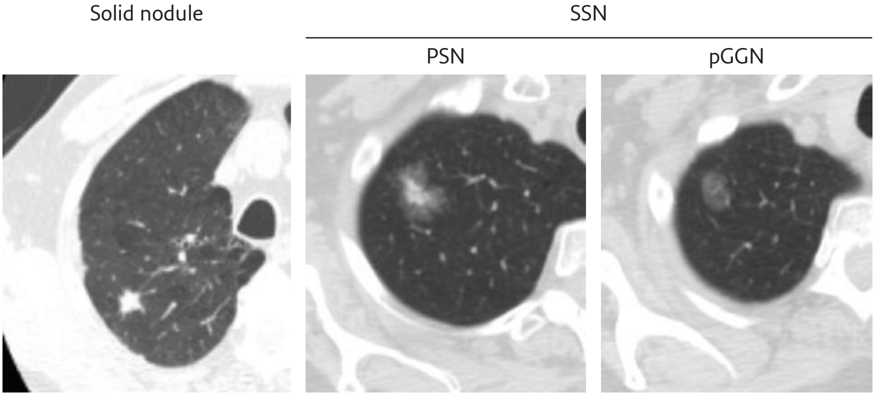


Figure 1. The classification of pulmonary nodules. Reproduced and modified from Callister et al. *(2015), with permission from the publisher.*

a fissure (figure 2). They represent intrapulmonary lymph nodes and require no follow-up provided they do not have atypical features. Such features include irregular or spiculated margins, eccentric or lobulated shape and distortion of the fissure (figure 3). Follow-up is also optional or not recommended for small nodules. In the BTS guideline nodules below 5 mm diameter or <80 mm^3 volume (the preferred measurement method) and in the Fleischner Society guidelines nodules <6 mm diameter (actually 5.5 mm, as measured to nearest 1 mm) have optional follow-up in high-risk people. Both guidelines recommend the same diameter thresholds for SSN, except the Fleischner Society guidelines recommend interval imaging for multiple SSNs with a diameter below 5 mm. Exceptions to these follow-up thresholds are cases where there is a previous history of malignancy, where follow with interval imaging may be appropriate, allowing for the site of the primary, the stage, and the success of and time since treatment. Another exception is where nodules were not seen on a previous CT scan. These have a high risk of malignancy and the thresholds applied are 3 mm diameter or 27 mm^3. Smaller nodules associated with cysts should also be followed up as these are more often malignant (figure 3).

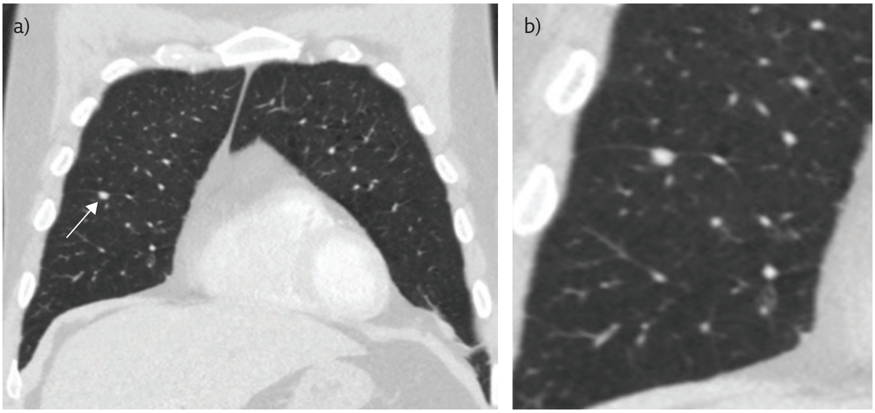


Figure 2. A perifissural nodule characterised by multi-planar reconstruction. a) Coronal image and b) close-up. The nodule (arrow) is associated with a fissure and is lentiform and has sharp angular margins. This nodule is benign and is very likely to be an intrapulmonary lymph node.

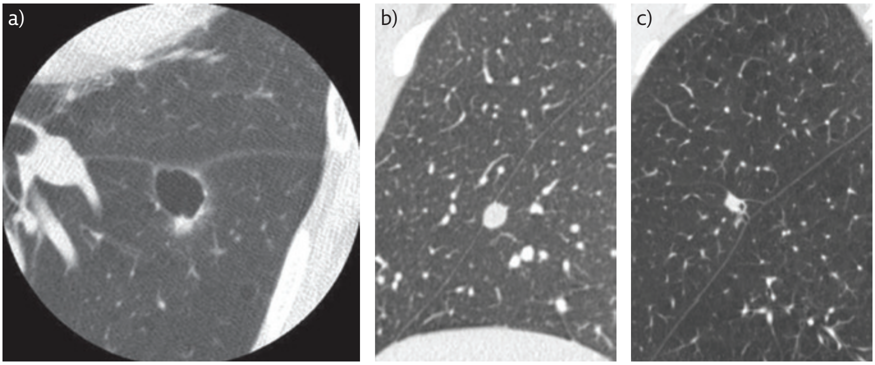


Figure 3. Exceptions to the rule. a) A small nodule associated with a cyst, these require a 3-month interval CT and further follow-up if stable. This nodule was an adenocarcinoma. b, c) Malignant perifissural nodules; these were adenocarcinomas. They both have spiculated margins, and b) shows bulging margins and c) distortion of the fissure.

Surveillance and referral

Further management depends on the assessment of the risk of malignancy. There is debate about what risk should be regarded as 'low' and 'high'. The BTS guideline suggests <10% is low and >70% high, while other guidelines suggest <5% and >65%. People with low-risk nodules can be followed by interval imaging and those with high risk nodules might be referred for treatment. Those with intermediate risk can have further investigations. Surveillance is recommended for nodules that are <8 mm diameter or <300 mm^3 (BTS) or <250 mm^3 (Fleischner Society). The BTS guideline specifies a preference use of fixed interval follow-up of 3 and 12 months (as in the NELSON and UKLS trials) and mandates volumetry as the preferred method of assessment of nodules, only relying on diameter when volumetry is not possible. While the Fleischner Society acknowledges that volumetry is more accurate, diameter measurements are preferred, and follow-up intervals are variable and left to the discretion of the clinician. The BTS guideline also recommends a further step in defining low risk using the Brock risk prediction model for nodules >8 mm diameter. All patients with nodules that have a risk of <10% enter surveillance with a 3-month interval CT.

Further management is according to whether the nodules show interval growth. The BTS guideline recommends referral for investigation if the volume doubling time (VDT) is <400 days, optional surveillance or referral for those with VDT of 400–600 days and optional follow-up for VDTs >600 days.

Further investigation

Nodules with an intermediate or high risk warrant clinical workup. While all the recent guidelines recommend the use of positron emission tomography (PET)-CT, the purpose is different. The BTS guideline specifically recommends re-evaluation of risk after a PET using the Herder multivariable model, which has excellent performance in larger nodules (>8 mm). This allows some patients to go back to surveillance and others to go directly for definitive treatment. Other guidelines do not suggest that PET is used to modify risk and merely recommend it as part of the general work-up. People with intermediate risk nodules are best offered pretreatment biopsy because of the uncertainty. The most accurate technique is CT-guided transthoracic lung biopsy, although other techniques such as electromagnetic navigation bronchoscopy and radial endobronchial ultrasound are used. Conventional bronchoscopy and bronchial washing can be performed prior to treatment to detect infection and, although usually negative, it has the potential to avoid an unnecessary procedure. Other imaging modalities such as MRI and single photon emission CT do not have a significant role in nodule management.

Invasive management of SSNs

SSNs are known to have a good prognosis and both the Fleischner Society and BTS recommend a more conservative approach, favouring surveillance over definitive treatment. For pGGNs even growth of a nodule does not mandate treatment with both guidelines giving the option of surveillance. This is supported by recent evidence from the Early Lung Cancer Action Programme. Clear growth of the solid component of PSNs, pleural indentation and a bubble-like appearance are predictors of malignancy. Although the BTS and Fleischner Society favour definitive treatment for enlarging PSNs, evidence is mounting that many still have an excellent prognosis and it is likely that future guidelines will recommend a period of observation prior to intervention. Where malignancy has been confirmed, the staging of a PSN is now based on the size of the solid component of the nodule, mapping to the TNM (tumour, node, metastasis) classification of malignant tumours eighth edition T stage criteria for solid nodules. In addition, there is stage T1mi where the solid component is <5 mm. This reflects the correlation of the solid component with the extent of the invasive disease; lesions <5 mm are most often minimally invasive adenocarcinoma.

Treatment

Decisions on treatment should preferably be made by a multidisciplinary team with ability to offer the patient a choice, where appropriate. For people with high risk nodules, or those who elect to have treatment, a surgical approach is preferred for those who are fit enough. Most guidelines allow resection without biopsy, but specify that there should be a frozen section prior to a definitive ‘cancer operation’. The BTS guideline recommends that lobar or sub-lobar resection is performed and although the evidence was limited, prefer anatomical segmentectomy to wedge resection as a sub-lobar procedure. The Fleischner Society do not include recommendations on treatment. The BTS guideline also recommends therapy with curative intent without biopsy where it is deemed unsafe to carry out a biopsy and the patient is unfit for surgery. The BTS guideline states that treatment can go ahead if the nodule is proven to have a high probability of malignancy after PET. Waiting to establish whether there is growth adds nothing to the prediction of malignancy after PET-CT since the 2-fluoro-2-deoxy-ᴅ-glucose (FDG) uptake measures metabolic activity which also reflects growth. In addition, waiting for lesions to grow may result in stage progression so this practice can be harmful. Ablative therapy is the preferred nonsurgical treatment (stereotactic ablative body radiotherapy or microwave/radiofrequency ablation).

Patient information

The BTS guideline has a chapter dedicated to patient information, and following a review of the evidence, recommends that information about nodules and their management needs to be clear in respect of the chance a nodule is malignant, with particular emphasis on the high chance of a benign outcome where the risk is low as patients are likely to wrongly assume they have cancer. Information needs to be given in a form that patients can understand. Good communication is essential to ensure informed, shared decision making. For example, the decision to proceed with biopsy, treatment or surveillance can be recommended to patients, but the final decision will depend on their preference after giving due consideration to their fitness for treatment and overall prognosis. All of these factors need to be discussed. Surgery without biopsy should only proceed where there has been a detailed explanation, including the possibility of a benign outcome, which is documented, confirming the patient understands. Where nodules are referred for further work-up, the BTS guideline recommends a consultation with a lung cancer nurse specialist is offered.

Smoking cessation and symptoms

Detection of pulmonary nodules has been shown to increase the chance of smoking cessation so all patients who smoke should be given advice and assistance to help them quit. High risk patients remain at risk of lung cancer and should be warned or reminded of the red flag symptoms and advised to seek medical advice if they have these. Patients may be sufficiently reassured by a clear CT to delay presentation. This is especially important when patients are discharged.

Technical and measurement standards

Both the BTS and Fleischner Society provide similar recommendations on standards for CT, recommending low radiation thin section (preferably 1.25 mm or less) volumetric CT. In addition, the use of maximum intensity projections and multi-planar reconstruction is recommended. The BTS guideline prefers volumetry, whereas the Fleischner Society give this as an option with a detailed separate paper on average nodule diameter measurement (Bankier *et al*., 2017). This specifies significant growth as an increase in the average of the two maximum diameters rounded to the nearest millimetre measured in two out of three orthogonal planes. Growth is defined as significant where the diameter has increased by 2 mm in the Fleischner Society guidelines. However, a 1 mm increase in diameter in a 6 mm nodule over an interval of 3 months equates to a 60% increase in volume and a VDT of 133 days. Where volumetry is employed, the same software should be used for comparisons during surveillance. Version updates should include information about the potential for less reliable comparisons. Growth is defined as at least a 25% increase in volume, accounting for the inherent factors that influence the accuracy of this measurement.

Service implications

Nodule management should be guideline driven and the fact that most patients can be safely managed by low dose surveillance means that hospital visits can be minimised by following a protocol for written and verbal communication. Nodules are best managed by a multidisciplinary team including a radiologist, a pulmonologist and an administrator.

Further reading

- Bankier AA, *et al.* (2017). Recommendations for measuring pulmonary nodules at CT: a statement from the Fleischner Society. *Radiology*; 285: 584–600.
- Callister MEJ, *et al.* (2015). British Thoracic Society guidelines for the investigation and management of pulmonary nodules. *Thorax*; 70: Suppl. 2, ii1–ii54.
- Gould MK, *et al.* (2013). Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*; 143: Suppl., e93S–e120S.
- MacMahon H, *et al.* (2017). Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. *Radiology*; 284: 228–243.

Pleural and chest wall tumours

Arnaud Scherpereel

Pleural and chest wall malignancies are quite common diseases in our practice. Malignant pleural effusions (MPEs) and pleural metastases are much more frequent than primary tumours of these tissues (mesothelioma, sarcoma, lymphoma, *etc.*). Primary chest wall tumours are a heterogeneous group of rare (~5% of all thoracic malignancies; 2% of all primary tumours), malignant (60% of cases) or benign tumours that may arise from bones or soft tissues, but having similar diagnostic and therapeutic issues.

The majority of patients with MPE are symptomatic, with breathlessness the most common symptom. The presence of MPE usually represents advanced or metastatic disease, and consequently survival is poor, ranging from a median of 3 months to 12 months depending on underlying patient and tumour factors. The focus of treatment is inevitably palliative and aimed at relieving symptoms.

Epidemiology and pathogenesis

Malignant mesothelioma is a rare cancer but with increasing incidence worldwide, which involves the pleura in 90% of cases. In fact, malignant pleural mesothelioma (MPM) diagnosis may occur up to 50 years after exposure to the main factor involved in MPM pathogenesis, occupational asbestos (usually found in >80% of male cases but <50% of females by occupational survey). Asbestos use was banned in most Western countries in the 1980s–1990s but sadly, it is still extracted and/or used in many countries in the rest of the world.

Key points

- Malignant pleural effusions (MPEs) are much more frequent than primary pleural or chest wall tumours.
- Diagnostic strategy includes cytology on pleural effusion, but a firm and reliable diagnosis of cancer is based on histology, usually best obtained by biopsies during thoracoscopy.
- Talc pleurodesis by thoracoscopy and indwelling pleural catheter represent two excellent alternatives of local treatment of recurrent or massive MPEs, and can be combined if necessary.
- Figures 1 and 2 summarise a proposal for MPE and malignant pleural mesothelioma management.

Pleural metastases and MPEs

Pleural tumour involvement may result from a direct invasion from adjacent structures (lung, chest wall, *etc*.), blood dissemination or, more often, from tumour emboli to the visceral pleura with secondary seeding to the parietal pleura (lung cancer). Effusion may be due to the pleural tumour lesions or to a lymphatic blockade at the mediastinal level. MPEs also depend on interactions between tumour cells and mesothelial cells through growth factors such as vascular endothelial growth factor, that increase vascular permeability and angiogenesis.

MPEs are common and found in up to 15% of patients with malignancy. In half of these cases, MPEs may reveal the cancer. Neoplasias responsible for pleural metastases and/or MPE are mostly lung cancer (30% of cases) or breast cancer (10–15%), but other cancers include carcinomas (ovarian, gastric, *etc*.) or noncarcinoma proliferations such as lymphoma, sarcoma, melanoma, seminoma or thymoma. The incidence of MPE is likely to rise as global cancer incidence increases and overall survival improves. Pleural effusion is the main clinical element, but it is not found in all pleural malignancies. Moreover, pleurisy is not systematically synonymous with MPE in cancer patients, because it may be induced by other mechanisms, such as pneumonia and/or atelectasis due to bronchial obstruction, transudate induced by severe denutrition or cardiac failure, or even drug- or radiotherapy-induced effusion. Therefore, the diagnostic strategy may differ depending on whether the patient has a cancer background, but should always rely on cytology or, better still, on histology.

Lymphoma and chest wall sarcoma

More than half of malignant tumours of the chest wall are metastatic lesions from distant organs or invasion from contiguous structures. Initial thoracic involvement of lymphoma is common but mostly involves the mediastinum. Lung parenchyma and/or pleural localisations are less frequent and need to be histologically proven because they modify the staging and prognosis of the tumour. Primary soft-tissue sarcoma of the chest wall is a rare disease (4%–10% of soft-tissue sarcomas). The most common sarcomas of the chest wall are chondrosarcoma, followed by osteosarcoma, Ewing's sarcoma, primitive neuroectodermal tumour, malignant fibrous histiocytoma and fibrosarcoma. Primary pleural and pulmonary sarcomas are rare. The chest wall is also a well-known site of radiation-induced sarcoma.

Prognosis

The global prognosis of patients with pleural metastases or MPM is poor (median overall survival ≤12 months). However, survival may differ according to multiple baseline factors predicting prognosis, including the primary cancer type (better outcome for breast cancer or lymphoma), presence of favourable markers (epithelial growth factor receptor mutation, ALK amplification or other oncogenic driver in non-small cell lung cancer, responders to immunotherapy *etc*.), tumour stage, ECOG (Eastern Co-operative Oncology Group) performance status (PS), and inflammatory markers in blood and pleural fluid. Only the patient's PS and histological subtype are recognised as prognostic factors for the management of MPM in routine, with poorer outcomes for patients with non-epithelioid MPM subtype and/or PS > 1.

Although multiple prognostic tools have been published, only the LENT (pleural fluid lactate dehydrogenase, ECOG PS, neutrophil/lymphocyte ratio, tumour type) score has been validated in MPE, and Brims' decision tree is the most clinically useful in mesothelioma as underlined by the 2018 European Respiratory Society (ERS)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines on MPE

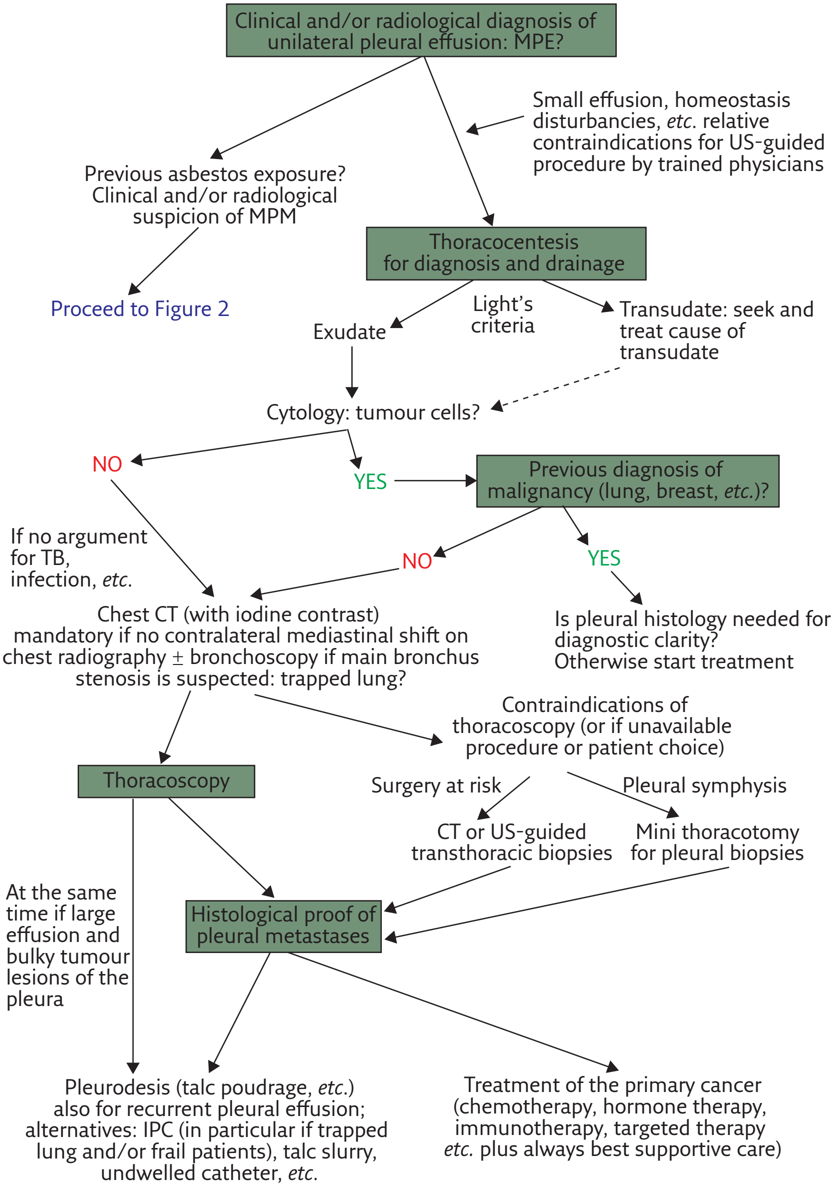

Clinical and/or radiological diagnosis of unilateral pleural effusion: MPE?
Small effusion, homeostasis disturbancies, *etc.* relative contraindications for US-guided procedure by trained physicians
Previous asbestos exposure? Clinical and/or radiological suspicion of MPM
Proceed to Figure 2
Thoracocentesis for diagnosis and drainage
Light's criteria
Exudate
Transudate: seek and treat cause of transudate
Cytology: tumour cells?
NO
YES
Previous diagnosis of malignancy (lung, breast, *etc.*)?
If no argument for TB, infection, *etc.*
NO
YES
Chest CT (with iodine contrast) mandatory if no contralateral mediastinal shift on chest radiography ± bronchoscopy if main bronchus stenosis is suspected: trapped lung?
Is pleural histology needed for diagnostic clarity? Otherwise start treatment
Contraindications of thoracoscopy (or if unavailable procedure or patient choice)
Thoracoscopy
Surgery at risk
Pleural symphysis
CT or US-guided transthoracic biopsies
Mini thoracotomy for pleural biopsies
At the same time if large effusion and bulky tumour lesions of the pleura
Histological proof of pleural metastases
Pleurodesis (talc poudrage, *etc.*) also for recurrent pleural effusion; alternatives: IPC (in particular if trapped lung and/or frail patients), talc slurry, undwelled catheter, *etc.*
Treatment of the primary cancer (chemotherapy, hormone therapy, immunotherapy, targeted therapy *etc.* plus always best supportive care)

Figure 1. Proposed management for MPE.

management. Sarcomas have a variable prognosis, with a reported 5-year survival from 15 to 90%, depending mostly on the localisation, grade and differentiation of the tumour, and the possibility of achieving an early wide resection of the sarcoma.

Diagnosis

Clinical signs

Dyspnoea on exertion and dry cough are the most common signs of MPE. Dyspnoea is usually progressive and more marked as the effusion becomes

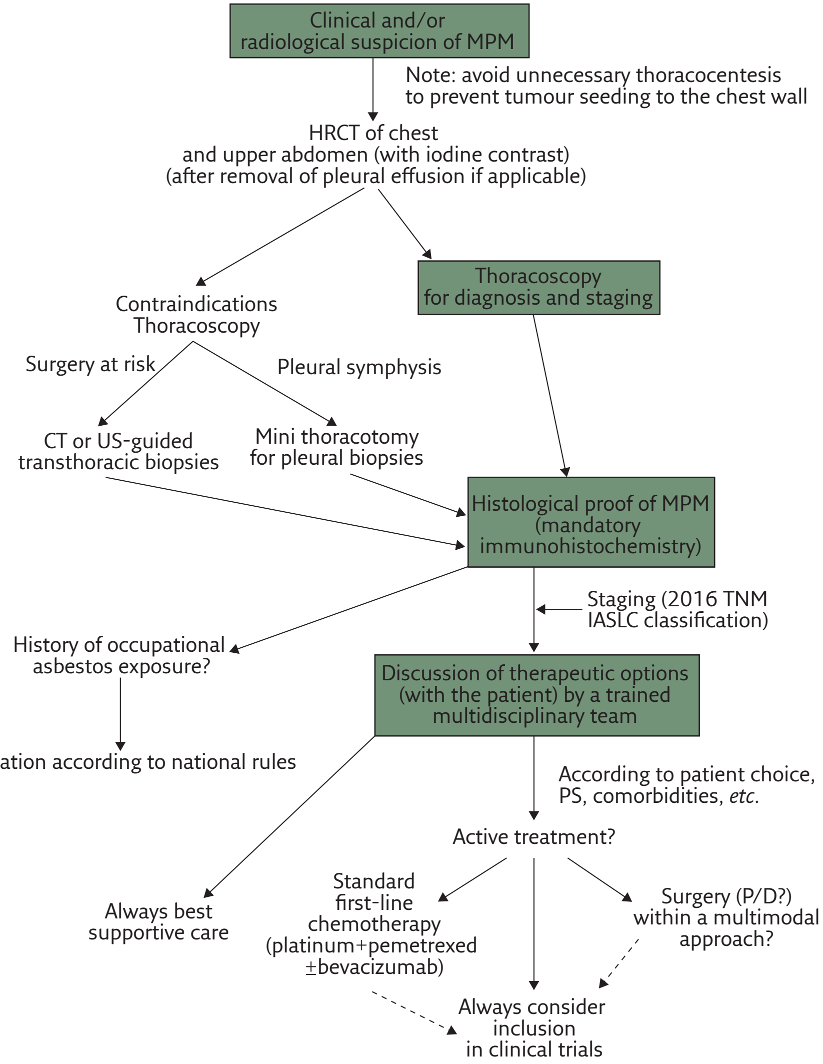

Clinical and/or radiological suspicion of MPM
Note: avoid unnecessary thoracocentesis to prevent tumour seeding to the chest wall
HRCT of chest and upper abdomen (with iodine contrast) (after removal of pleural effusion if applicable)
Contraindications Thoracoscopy
Thoracoscopy for diagnosis and staging
Surgery at risk
Pleural symphysis
CT or US-guided transthoracic biopsies
Mini thoracotomy for pleural biopsies
Histological proof of MPM (mandatory immunohistochemistry)
Staging (2016 TNM IASLC classification)
History of occupational asbestos exposure?
Discussion of therapeutic options (with the patient) by a trained multidisciplinary team
Reparation according to national rules
According to patient choice, PS, comorbidities, etc.
Active treatment?
Always best supportive care
Standard first-line chemotherapy (platinum+pemetrexed ±bevacizumab)
Surgery (P/D?) within a multimodal approach?
Always consider inclusion in clinical trials

Figure 2. Proposed management for MPM. P/D: pleurectomy/decortication.

larger, but it may be also modulated by other factors, *i.e.* bronchus obstruction, carcinomatous lymphangitis or associated (pulmonary or cardiac) comorbidities. Chest pain suggests chest wall involvement. Other signs may include weight loss, anorexia, asthenia, haemoptysis (lung cancer), adenopathy, peritoneal effusion, *etc*. However, MPE or MPM may be diagnosed in asymptomatic patients by routine chest imaging. A diagnosis of MPM should not be based on nonspecific and usually late clinical signs. However, the association of chest pain, thoracic 'shrinkage', and/or a unilateral pleural effusion or thoracic mass in asbestos-exposed patients may suggest this diagnosis.

There are no reliable clinical features for distinguishing benign from malignant chest wall tumours. A palpable mass and chest pain are common in both groups of tumours. A firm diagnosis is often obtained only after resection.

Imaging

Pleural metastases usually exhibit a moderate-to-large, nonloculated and unilateral pleural effusion. MPE may be associated with an irregular pleural thickening. Typically, this large pleural effusion induces a contralateral mediastinal shift. If not, one should suspect an obstruction of a main bronchus by lung cancer or metastasis, a fixed mediastinum caused by the cancer and/or lymph nodes, an extensive tumour infiltration of the ipsilateral lung mimicking a large effusion, or MPM.

In MPM patients, chest radiography or, better, CT typically shows a nonspecific, unilateral (95% of cases) pleural effusion with or without mediastinal shift. More rarely, pleural thickening or mass, without pleurisy, may be observed. Pleural plugs are quite common in asbestos-exposed subjects; more rarely asbestos-induced pulmonary fibrosis may be found with MPM. Definitive diagnosis of MPM is not possible by CT but this is recommended for diagnosis and staging (after removal of pleural effusion if applicable). MRI is mostly useful to assess the tumour extent into the diaphragm and chest wall. ^{18}F-fluorodeoxyglucose positron emission tomography (PET) usually shows hypermetabolism of pleural mesothelioma, metastatic adenopathy and metastasis, but should not currently be performed for the diagnosis of MPM. Pleural hypermetabolism is also induced by talc pleurodesis. PET may be helpful for the staging of pleural malignancies or in the search for primary cancer.

Although histological analysis is almost always required for accurate diagnosis, imaging (CT or better, MRI) is an important step for the staging of chest wall sarcomas. Moreover, several of these tumours have distinctive radiological features, allowing the radiologist to narrow the differential diagnosis.

Pathology and diagnostic procedures

In patients suspected of having MPE, a thoracocentesis is the first diagnostic step (American Thoracic Society (ATS)/ERS guidelines). Pleural fluid analysis usually finds an exudate according to Light's criteria but a transudate, which may be due to major hypoproteinaemia with cachexia or to malignant pericardial effusion, does not eliminate the diagnosis of MPE. Assessment of the pleural level of adenosine deaminase can yield false positive results in some cases of MPM or lymphoma, but may be helpful in countries with medium-to-high prevalence of TB. The diagnostic sensitivity of pleural cytology in MPE may vary depending on the extension of the pleural lesions and the primary cancer, from 62 to 90% in case series. Thus, in a patient with a history of cancer, cytology may be enough for the diagnosis of MPE and/or pleural metastases, and can also provide useful prognostic and therapeutic information. However, a diagnosis of MPM should not be based on cytology alone because of its poor sensitivity (30%) and specificity (potential confusion with reactive mesothelial cells or adenocarcinoma cells).

Closed, percutaneous needle (*e.g.* Abrams) pleural biopsies are quite easy to perform under local anaesthesia on an outpatient basis. However, due to the potentially scarce and irregular distribution of the tumour lesions in the pleural cavity, the positive yield of blind biopsies is low (30–40%), adding little to a negative cytology, except in countries with a high incidence of TB. CT- or ultrasound-guided biopsies have a better diagnostic sensitivity than blind biopsies in series of MPEs (70–80% sensitivity), but lower than that of thoracoscopy. They are not recommended for MPM diagnosis, except in patients for whom thoracoscopy (or mini thoracotomy with pleural symphysis) is contraindicated or rejected by the patient. If MPM is not clearly suspected, closed needle biopsies may first be proposed in young patients with pleural lesions and exudative, cytology-negative pleural effusion from countries with a relatively high prevalence of TB.

Medical (pleuroscopy) or surgical (video-assisted thoracoscopic surgery) thoracoscopy with multiple pleural biopsies is the 'gold standard' for obtaining a diagnosis of MPM or pleural metastasis, although in cases where initial biopsies yield inflammation, repeat biopsy or extended follow-up is usually required. Diagnostic accuracy is 90% and complications occur in 10% of cases. MPM or pleural metastasis will usually appear as nodules or masses of various diameters. Thoracoscopy is also useful for the staging of MPM and may permit talc pleurodesis in cases of massive and/or recurrent MPE. However, access to thoracoscopy may be limited in many places worldwide, as significant resources and expertise are required.

Immunohistochemistry is helpful in the search for the primary cancer for pleural metastases or to obtain an accurate diagnosis of mesothelioma, referring to the international classification of pleural tumours (World Health Organization, 2015). The epithelioid subtype is the most frequent mesothelioma subtype (≥60% cases).

Innovative technologies such as liquid biopsy may negate the need for biopsies in future, but further research is still needed to find out their potential role in routine clinical practice. Recently, soluble biomarkers have been sought to obtain an early and reliable diagnosis of pleural malignancies but, to date, none (including serum mesothelin) has been considered as valuable in routine practice. For chest wall tumours, pathological diagnosis is usually established on surgical specimens. It is important to distinguish low-grade *versus* high-grade tumours, as the latter have a much worse outcome in the literature.

Staging and pre-therapeutic assessment of MPM

It is recommended to use the IASLC Mesothelioma proposals for the eighth Edition of the TNM Classification for MPM, published in 2016, even if it is still unsatisfactory in describing tumour and node extent by current imaging procedures. Scherpereel et al. (2010) proposed a simple and sequential three-step pre-treatment assessment. Any active therapeutic strategy of MPM would require at least an updated chest and upper abdomen CT with iodine contrast before starting treatment. Further procedures (PET, *etc.*) would be indicated depending on clinical symptoms and/or if a multimodal treatment (including maximal tumour resection) is proposed.

Treatment

Treatment includes palliative local therapies, mostly to improve the patient's symptoms, and treatment of the primary cancer, depending on the nature of the malignancy, clinical status and wishes of the patient.

Treatment of primary cancer

MPM treatment, summarized in the 2010 ERS/ESTS guidelines and the 2018 British Thoracic Society (BTS) guidelines, still relies mostly on best supportive care (oxygen, pain relief, nutrition, *etc.*) associated with chemotherapy. There is limited evidence for the efficacy of 'radical' surgery for mesothelioma, except parietal pleurectomy in very early and rare stage IA disease. Maximal tumour resection (pleurectomy/decortication) is now preferred to extrapleural pneumonectomy because of the lower morbidity/mortality and better outcome when combined with chemotherapy and/or radiotherapy. Both surgical procedures should be performed only in clinical trials, in specialised centres and as a part of multimodal treatment. Pleurectomy/decortication can also be considered to achieve symptom control, especially in symptomatic patients with entrapped lung syndrome who cannot benefit from chemical pleurodesis. Palliative radiotherapy aimed at pain relief may be considered in the case of painful chest wall infiltration or nodules. Prophylactic radiotherapy to prevent subcutaneous metastasis developing along drainage channels or thoracocentesis tracts is no longer recommended in routine after two recent negative randomised trials.

When a decision is made to treat patients with chemotherapy, subjects with a good PS should be treated with first-line chemotherapy combining platinum and an antimetabolite (pemetrexed) with or without anti-vascular endothelial growth factor drug (bevacizumab) or could be included in clinical trials. No drug has been validated in second-line chemotherapy, and patients with a good PS should be proposed for clinical trials. Patients demonstrating prolonged symptomatic and objective response with pemetrexed-based first-line chemotherapy may be treated again with the same regimen in the event of relapse. Immunotherapy (anti-programmed death-1 (anti-PD-1)/programmed death ligand 1 (PD-L1)±anti-cytotoxic T-lymphocyte-associated protein-4 antibodies) exhibited promising results in relapsing MPM, but was not recommended yet in routine except pembrolizumab or nivolumab±ipilimumab by the US National Comprehensive Cancer Network guidelines. For tumour assessment and follow-up of MPM, only chest CT with iodine injection is recommended. The new 2018 revised Response Evaluation Criteria In Solid Tumours (RECIST) criteria (version 1.1) for MPM are the preferred guidelines for measuring response to treatment.

Pleural metastases

Treatment of metastatic cancer may rely on chemotherapy and/or hormone therapy, immunotherapy (*e.g.* NSCLC), or even targeted therapy, but also best supportive care in all cases. The choice of the drug(s) depends on the nature of the primary cancer, tumour PD-L1 expression for immunotherapy, or even the presence of a targetable oncogenic driver (epithelial growth factor receptor mutation *etc.*) for targeted therapies. Mediastinal radiotherapy may be combined with chemotherapy for lymphoma.

Chest wall sarcomas

The treatment of choice is an early, adequate and wide resection of the sarcoma. Reconstruction of the chest wall may be needed depending on the number of resected ribs but mostly depending on the location of the tumour (more frequently needed if anterior chest tumours). According to local protocols, (neo)adjuvant radiotherapy can be considered in particular for high grade sarcomas and/or in microscopic tumour infiltration (R1) cancers, or when narrow margins are expected or confirmed after tumour resection. There is no clear consensus for the use of chemotherapy, but it can be considered for high-grade sarcomas and advanced stage disease (as well as targeted therapies).

Local treatment

Recently published 2018 ERS/EACTS guidelines extensively address the management of MPE. Some of their conclusions are presented here. Pleurodesis is useful in treating a patient's symptoms and preventing recurrent effusions. Sterile talc is the most effective agent available for chemical pleurodesis and may be administered in the pleural space through a chest drain ('talc slurry') or, likely better, during thoracoscopy ('talc poudrage'). Surgical pleurodesis procedures are no more effective than talc, in particular for mesothelioma. Large-bore tubes (*e.g.* 24 French (F)) are associated with higher pleurodesis success rates in talc pleurodesis than smaller drains (*e.g.* 12F), with nonsteroidal drugs as an effective analgesia option that does not lower pleurodesis rates. Pleurodesis is most effective when performed early in the disease process before effusions have become loculated and/or the lung has become fixed and is unable to expand fully, but it should not be performed before sufficient tissue for diagnosis has been obtained. Criteria for talc pleurodesis are a sufficient PS (≥2), an estimated survival of at least 3 months, an established diagnosis of the tumour and no arguments for either a trapped lung (suspected if a pneumothorax persists after thoracocentesis) or an endobronchial tumour (massive pleural effusion without a contralateral mediastinal shift). This may justify a bronchoscopy or a pleural manometry before pleurodesis. To decrease the risk of pleurodesis failure in MPE, it is recommended to use 4 g talc after complete aspiration of pleural effusion. Benign usual side-effects of talc (fever and chest pain) were observed with both methods, but no acute respiratory distress syndrome or death.

Alternatives to talc pleurodesis are repeated pleural punctures or, better, indwelling pleural catheters (IPCs). The 2018 ERS/EACTS Task Force concluded that IPCs appear to be as effective at relieving MPE symptoms as talc pleurodesis and are associated with reduced time in hospital, although adverse event rates appear to be higher than for talc, even if dedicated prospective trials are needed to fully evaluate the utility of IPCs in trapped lung, and to evaluate surgical interventions and the role of fibrinolytic therapy. Thus, most current guidelines consider IPCs an effective, ambulatory procedure for symptomatic, recurrent MPE. IPCs can be used as a first-line treatment, and should be favoured for patients with trapped lung, or those who are not considered good candidates for chemical pleurodesis because of short life expectancy. Spontaneous pleurodesis may be obtained by IPC without mortality or major morbidity in nearly half of the cases when pleural drainage is performed *via* the catheter every other day, or even up to 70% in MPE patients fit for pleurodesis. Finally, to date, there is no robust evidence to support the use of any oncological therapy as an alternative to mechanical drainage, although further research is required.

Further reading

- Bhatnagar R, *et al.* (2018). Outpatient talc administration by indwelling pleural catheter for malignant effusion. *N Engl J Med*; 378: 1313–1322.
- Bibby AC, *et al.* (2018). ERS/EACTS statement on the management of malignant pleural effusions. *Eur Respir J*; 52: 1800349.
- Carter BW, *et al.* (2015). MR imaging of chest wall tumors. *Magn Reson Imaging Clin N Am*; 23: 197–215.
- Clive AOJ, *et al.* (2016). Interventions for the management of malignant pleural effusions: a network meta-analysis. *Cochrane Database Syst Rev*; 5: CD010529.
- Feller-Kopman D, *et al.* (2018). Pleural disease. *N Engl J Med*; 378: 740–751.
- Muruganandan S, *et al.* (2018). Aggressive *versus* symptom-guided drainage of malignant pleural effusion via indwelling pleural catheters (AMPLE-2): an open-label randomised trial. *Lancet Respir Med*; 6: 671–680.
- Scherpereel A, *et al.* (2010). Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for management of malignant pleural mesothelioma. *Eur Respir J*; 35: 479–495.
- Scherpereel A, *et al.* (2018). Novel medical therapies for malignant pleural mesothelioma: a review. *Lancet Oncol*; 19: e161–e172.
- Travis WD, *et al.* (2015). WHO Classification of Tumors of the Lung, Pleura, Thymus and Heart. 4th Edn. Geneva, WHO Press.
- Woolhouse I, *et al.* (2018). British Thoracic Society Guideline for the investigation and management of malignant pleural mesothelioma. *Thorax*; 73: Suppl 1, i1–i30.

Mediastinal tumours

Lawek Berzenji, Laurens Carp, Jeroen M. Hendriks, Patrick Lauwers and Paul E. Van Schil

Variety of compartments and organs

Currently, the mediastinum is divided into three compartments: a prevascular (anterior), a visceral (middle) and a paravertebral (posterior) compartment. This clinical classification, which has been accepted by the International Thymic Malignancy Interest Group, is based on anatomic boundaries that are clearly identified on CT. All three compartments are bound superiorly by the thoracic inlet and inferiorly by the diaphragm.

The prevascular mediastinum is bound anteriorly by the manubrium of the sternum, posteriorly by the anterior aspect of the pericardium, and laterally by the pleurae. The major contents are part of the involuted thymus in adults, the left brachiocephalic vein and retrosternal lymph nodes draining the mammary gland.

The visceral mediastinum is bound anteriorly by the pericardial sac and posteriorly by a virtual vertical line running along the thoracic vertebral bodies, 1 cm posteriorly to the anterior margin of the spine. The major contents of this compartment are the heart, the large vessels, the oesophagus and the bifurcating trachea.

The posterior paravertebral compartment is bound anteriorly by the posterior boundaries of the visceral compartment, and a virtual vertical line along the posterior margin of the chest wall at the lateral margin of the transverse processes of the thoracic spine. The posterior compartment mainly contains paravertebral soft tissues.

Variety of histological types and tumours

In both young and old patients, a range of primary tumours and cysts are encountered in the mediastinum; these are summarised in table 1. Metastases may also occur in the mediastinum.

Key points

- The mediastinum, which is defined as the anatomical compartment between both lungs, is a fascinating region due to its surprising complexity and variety.
- Mediastinal tumours are characterised by a wide variation in clinical presentation, histological features and treatment options.
- A multidisciplinary approach is necessary to determine optimal treatment.
- Surgical treatment should aim at complete resection.

Table 1. Primary tumours and cysts frequently encountered in the mediastinum

Compartment	Benign lesions	Mediastinal masses[#]	Malignant tumours	Mediastinal masses[#]
Prevascular	Thyroid goitre	20–40%, age >40 years	Thymoma	15–25%, age 20–39 years; 50%, age >40 years
			Lymphoma	25% (13% HD, 12% NHL)
	Mature teratoma	25%, age 10–19 years; 10–15%, age 20–49 years	Germinomatous GCT	11% (4% seminoma, 7% non-seminomal GCT)
	Pleuropericardial cysts	<5%		
	Thymic cyst	<5%		
Visceral[¶]	Bronchogenic cyst		Lymphoma	
	Lymphadenopathies		Metastases	
			Lymphadenopathies	
Paravertebral[¶]	Enterogenic cysts		Malignant neurogenic tumours	
	Benign neurogenic tumours			

GCT: germ-cell tumour; HD: Hodgkin disease; NHL: non-Hodgkin lymphoma. [#]: per compartment %; [¶]: no precise figures are available.

Variety of symptoms

Mediastinal tumours can grow to a large size before any symptoms appear and the clinical presentation varies depending on the type of mediastinal lesion. Large masses can cause physical pressure on surrounding structures resulting in symptoms such as hoarseness, dyspnoea, dysphagia and superior vena cava syndrome. For thymoma, an extensive clinical evaluation is necessary as 30–50% of cases present with a paraneoplastic syndrome. Myasthenia gravis (MG), hypogammaglobulinaemia and pure red cell aplasia are the most common paraneoplastic syndromes observed in patients with thymoma. Other possible disorders include neuromyotonia, limbic encephalitis, polymyositis, subacute hearing loss, psychosis, sleep disorders and several cutaneous disorders.

MG is an immune-mediated disorder of neuromuscular transmission caused by antibodies targeting proteins of the neuromuscular junction and is characterised by weakness of striated muscle. Characteristic symptoms are rapid muscle fatigue, ptosis and double vision. Hypogammaglobulinaemia is a disorder which is characterised by decreased levels of serum immunoglobulin G resulting in an impaired adaptive immune response. Clinical manifestations include recurrent, chronic or atypical

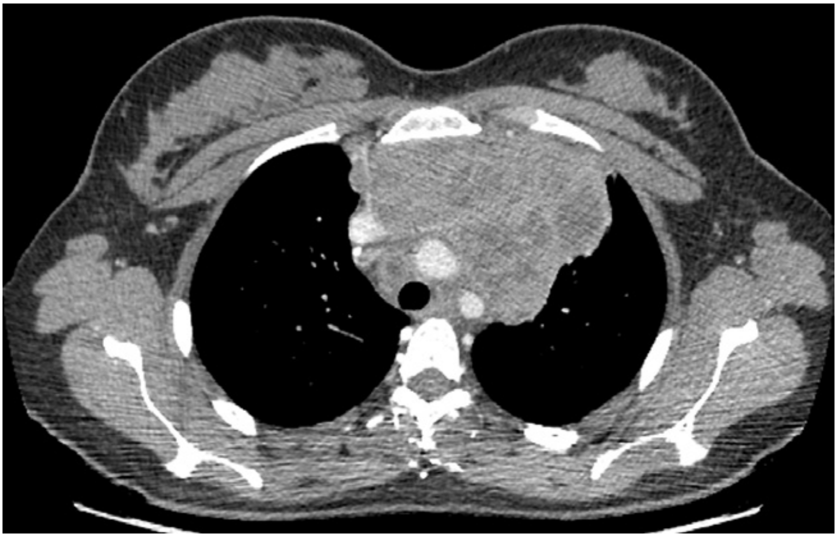


Figure 1. Large prevascular mediastinal mass in a 27-year-old female patient on chest CT. Diagnosis of non-Hodgkin B-cell lymphoma was made by anterior mediastinotomy.

infections often involving the respiratory tract. Pure red cell aplasia is a syndrome in which patients present with normocytic normochromic anaemia, reticulocytopenia and a marked decrease of erythroid precursors in bone marrow. Symptoms are usually associated with anaemia and can vary between patients. Lymphoma is a common anterior mediastinal lesion, predominantly found in women aged <40 years. In men, the proportion of lymphoma is relatively smaller with regards to anterior mediastinal lesions. Hodgkin disease and mediastinal large cell non-Hodgkin lymphoma are the most common types found in the prevascular mediastinum (figure 1). In patients aged <20 years, lymphoblastic non-Hodgkin lymphoma should also be considered when a lymphoma is suspected. Possible clinical symptoms of lymphoma include the typical 'B' symptoms such as weight loss, fever and night sweats. Other possible manifestations include fatigue, pruritus and, very commonly, lymphadenopathies in the cervical, supraclavicular and axillary regions.

Extragonadal germ-cell tumours (EGCTs) are lesions that occur predominantly in men and are most likely caused by a misplacement of gonadal cells during embryogenesis. The anterior mediastinum is the most common localisation and accounts for 50–70% of all EGCTs. Malignant non-teratomatous mediastinal EGCTs are divided into seminomas and non-seminomas. The clinical presentation of mediastinal EGCTs varies and is usually nonspecific. Possible symptoms are chest pain, dyspnoea, cough, fever, fatigue and a superior vena cava syndrome. Testicular atrophy, cryptorchidism, inguinal hernias and simultaneous occurrence of Klinefelter syndrome have been reported as well.

Variety of diagnostic means

Imaging is a crucial part in establishing a presumptive diagnosis and determining which subsequent diagnostic tests are necessary. Although in most cases a chest radiograph is performed initially as it is widely available and relatively inexpensive, this imaging modality rarely provides a definitive diagnosis. Chest CT, MRI and positron emission tomography (PET) provide clinicians a more accurate anatomical

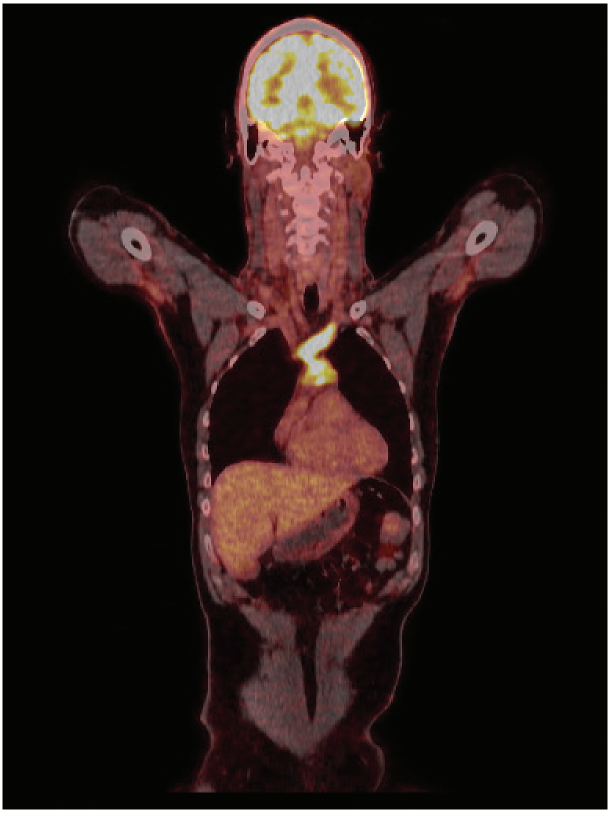


Figure 2. Frontal PET-CT image showing a prevascular tumour invading the superior vena cava and left brachiocephalic vein in a 48-year-old male patient. Immediate surgery was performed with venous reconstruction. The final diagnosis was thymoma B3.

delineation of the tumour and more insight to propose a specific differential diagnosis (figures 1–3). CT with intravenous contrast remains the imaging modality of choice in the diagnosis of mediastinal masses due to its widespread availability, relatively low cost and imaging acquisition speed. Chest CT scans have a high accuracy for determining the size, specific location and possible extension of mediastinal lesions into adjacent organs or structures. Furthermore, it has been shown that with a number of imaging features, clinicians and radiologists are often able to differentiate between different mediastinal lesions. The main disadvantage of CT is the use of a relatively high radiation dose and a lower accuracy in distinguishing solid from cystic masses. When a cystic mass is suspected, MRI will often be more useful given its superior tissue-contrast resolution. Due to the absence of ionising radiation, MRI can also be a useful imaging tool for children and adults for whom long-term follow-up is necessary. Moreover, specific modalities such as chemical shift and diffusion-weighted MRI are gaining popularity in recent years as they provide additional information in characterising the type of mediastinal mass. Undoubtedly, novel techniques and improvements will lead to an increasingly important role of MRI in the diagnosis of mediastinal masses in the near future.

Specific tumour markers may aid in the diagnostic workup of mediastinal masses. EGCTs and thymomas are known to produce specific serum markers and antibodies.

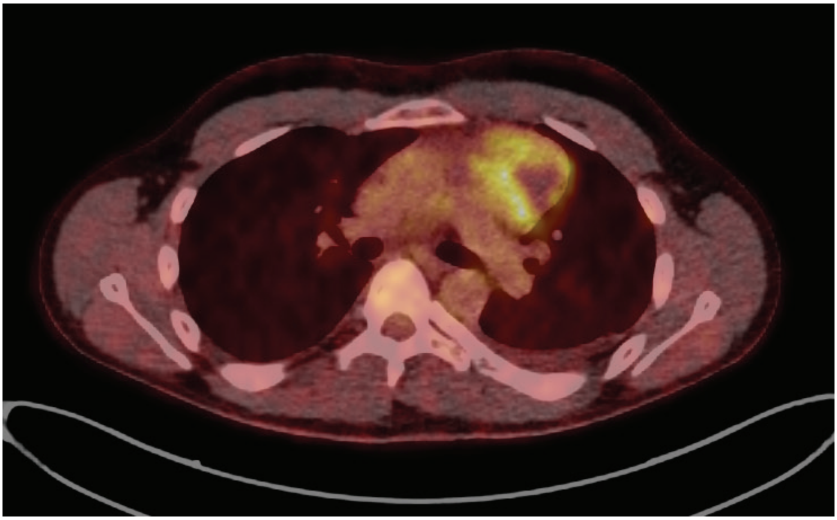


Figure 3. Transversal PET-CT image demonstrating a locally invasive prevascular tumour in a 30-year-old male patient. Diagnosis of thymoma B1 was made by anterior mediastinotomy. The patient was treated by induction chemotherapy followed by surgical resection by sternotomy.

Mediastinal EGCTs secrete hormones and cell products that are largely similar to the gonadal germ-cell tumours. α-fetoprotein, β-human chorionic gonadotropin and lactate dehydrogenase are the most important serum markers in the workup of EGCTs. For thymic epithelial tumours comprising thymoma and thymic carcinoma, there are currently no recognised hormonal or cell products that can be detected in blood serum. However, a large number of thymic epithelial tumours are associated with the production of autoantibodies and autoimmune disorders. For thymoma antibodies targeting acetylcholine receptors, muscle-specific tyrosine kinase, titin and ryanodine receptors are associated with diseases such as MG, Goodpasture's syndrome, pure red cell aplasia and Hashimoto thyroiditis. When MG is suspected, additional tests besides serologic testing for autoantibodies are often necessary as well. Electrodiagnostic studies such as repetitive nerve stimulation and single-fibre electromyography are useful supplements to immunological studies and may be used to confirm diagnosis of MG.

After initial work-up, a precise histological diagnosis is often necessary and may be obtained by CT-guided puncture, endoscopic or endobronchial ultrasound, mediastinoscopy, mediastinotomy or video-assisted thoracic surgery. In the case of suspicion of lymphoma, germ cell tumour or thymoma, large biopsies are often required as needle biopsies do not always provide conclusive results. Well-circumscribed tumours that are resectable in functionally operable patients should be excised at once so not to breach the surrounding capsule and to avoid spilling of tumour cells. Table 2 provides an overview of the most common mediastinal masses and the preferred initial histological diagnostic methods. For thymic epithelial tumours a specific tumour, node, metastasis (TNM) classification has been introduced that should be applied worldwide from 2018 onwards (table 3). Specific histological types for thymoma include type A, mixed AB, B1, B2 and B3.

Variety of therapeutic strategies

Resectable lesions are treated by surgical excision when deemed necessary. For small, asymptomatic mediastinal cysts that do not compress adjacent structures,

Table 2. Common mediastinal masses and need for pre-treatment histological diagnosis

Type of mediastinal mass	Pre-treatment histological diagnosis needed	Preferred initial histological diagnostic method
Thyroid goitre	–	NA
Thymoma	+/– (depending on presence of paraneoplastic syndromes and appearance on chest CT)	CT-guided TNB or anterior mediastinotomy
Lymphoma	+	CT-guided TNB, cervical mediastinoscopy or anterior mediastinotomy
Mature teratoma	–	NA
Germinomatous GCT	+	CT-guided TNB or anterior mediastinostomy

GCT: germ-cell tumour; TNB: transthoracic needle biopsy; NA: not applicable. +: pre-treatment histological diagnosis is needed; –: pre-treatment histological diagnosis not needed.

without atypical features or documented growth, a conservative wait-and-see approach may be considered. However, for enlarging or complicated mediastinal cysts, surgery is the standard treatment as it offers a definitive diagnosis and cure. In general, mortality and morbidity rates are very low for patients treated surgically for mediastinal tumours. In some cases, large resections are necessary to obtain a complete resection which is the most important prognostic factor (figure 4).

Table 3. 8th edition of the TNM classification for thymic epithelial tumours

Descriptor	Definition
T0	No evidence of primary tumour
T1	
a	Encapsulated or unencapsulated, with or without extension into mediastinal fat
b	Direct invasion of mediastinal pleura
T2	Direct invasion of the pericardium
T3	Direct invasion into any of the following: lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall or extrapericardial pulmonary artery or veins
T4	Direct invasion into any of the following: aorta, arch vessels, main pulmonary artery, myocardium, trachea, or oesophagus
N0	No nodal involvement
N1	Involvement of anterior (perithymic) nodes
N2	Involvement of deep intrathoracic or cervical lymph nodes
M0	No pleural, pericardial or distant metastasis
M1	
a	Separate pleural or pericardial nodule(s)
b	Pulmonary intraparenchymal nodule or distant organ metastasis

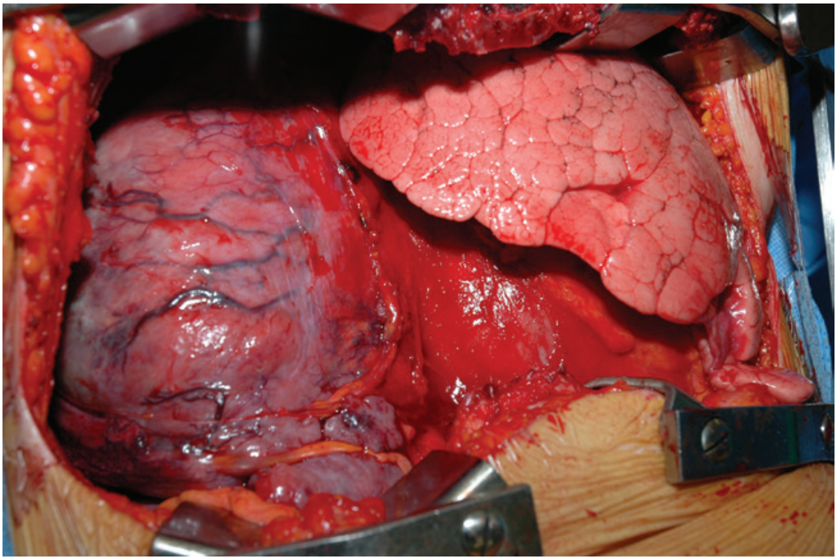


Figure 4. A large thymoma in the right hemithorax presenting with MG. The tumour was resected by a bilateral anterior thoracotomy (clam-shell incision).

Minimally invasive and even robotic techniques can be applied if a complete resection can be obtained by this approach. In case of incomplete resection or transcapsular invasion, adjuvant radio- or chemotherapy may be indicated. Inoperable lesions and lymphomas are treated by a combination of chemo- and radiotherapy. In selected cases, induction therapy may be a valid approach to downstage a locally aggressive tumour. Salvage surgery may be attempted in tumours that are no longer responsive to chemo- or radiotherapy. Long-term survival depends on histological type and completeness of resection.

Further reading

- Busch J, *et al.* (2016). Male extragonadal germ cell tumors of the adult. *Oncol Res Treat*; 39: 140–144.
- Carter BW, *et al.* (2014). A modern definition of mediastinal compartments. *J Thorac Oncol*; 9: Suppl 2, S97–S101.
- Carter BW, *et al.* (2014). Approaching the patient with an anterior mediastinal mass: a guide for clinicians. *J Thorac Oncol*; 9: Suppl. 2, S102–S109.
- Carter BW, *et al.* (2014). Approaching the patient with an anterior mediastinal mass: a guide for radiologists. *J Thorac Oncol*; 9: Suppl 2, S110–S118.
- Chiou-Tan FY, *et al.* (2015). Repetitive nerve stimulation and single-fiber electromyography in the evaluation of patients with suspected myasthenia gravis or Lambert–Eaton myasthenic syndrome: review of recent literature. *Muscle Nerve*; 52: 455–462.
- Date H (2009). Diagnostic strategies for mediastinal tumors and cysts. *Thorac Surg Clin*; 19: 29–35.
- Detterbeck FC, *et al.* (2014). The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposal for an evidence-based stage classification system for the forthcoming (8th) edition of the TNM classification of malignant tumors. *J Thorac Oncol*; 9: Suppl 2, S65–S72.

- Esme H, *et al.* (2011). Primary mediastinal cysts: clinical evaluation and surgical results of 32 cases. *Texas Heart Inst J*; 38: 371–374.
- Hammer MM, *et al.* (2019). Predictive features for anterior mediastinal mass diagnoses. *J Comput Assist Tomogr*; 43: 98–103.
- Juanpere S, *et al.* (2012). A diagnostic approach to the mediastinal masses. *Insights Imaging*; 4: 29–52.
- Liu Y, *et al.* (2014). Management of the primary malignant mediastinal germ cell tumors: experience with 54 patients. *Diagn Pathol*; 9: 33.
- Marino M, *et al.* (2019). Mediastinal tumor markers. Chapter 153. *In*: Locicero III J, *et al.*, eds. Shields' General Thoracic Surgery. 8th Edn. Philadelphia, Wolters Kluwer, pp. 1974–1999.
- Nicolle MW (2016). Myasthenia gravis and Lambert–Eaton myasthenic syndrome. *Continuum (Minneapolis, Minn);* 22: 1978–2005.
- Ong CC, *et al.* (2012). Imaging of anterior mediastinal tumours. *Cancer Imaging*; 12: 506–515.
- Priola AM, *et al.* (2016). Chemical shift and diffusion-weighted magnetic resonance imaging of the anterior mediastinum in oncology: current clinical applications in qualitative and quantitative assessment. *Crit Rev Oncol Hematol*; 98: 335–357.
- Thacker PG, *et al.* (2015). Imaging evaluation of mediastinal masses in children and adults: practical diagnostic approach based on a new classification system. *J Thorac Imaging*; 30: 247–267.
- Tomiyama N, *et al.* (2009). Anterior mediastinal tumors: diagnostic accuracy of CT and MRI. *Eur J Radiol*; 69: 280–288.

Obstructive sleep apnoea–hypopnoea syndrome

Wilfried De Backer

Definition

The obstructive sleep apnoea–hypopnoea syndrome (OSAHS) is characterised by recurrent episodes of partial or complete upper airway collapse during sleep. The collapse is highlighted by a reduction in or complete cessation of airflow despite ongoing inspiratory effort. Due to the lack of adequate alveolar ventilation that results from the upper airway narrowing, oxygen saturation may drop and partial pressure of carbon dioxide may occasionally rise. The events are mostly terminated by arousals. Clinical consequences are excessive daytime sleepiness related to the sleep disruption. Minimal diagnostic criteria have been defined for the OSAHS. Patients should have excessive daytime sleepiness that is not better explained by other factors or two or more of the following symptoms that also are not better explained by other factors: choking or gasping during sleep, recurrent awakenings from sleep, unrefreshing sleep, daytime fatigue and impaired concentration. Patients should all have more than five obstructed breathing events per hour during sleep. An obstructive apnoea or hypopnoea can be defined as an event that lasts ≥10 s and is characterised by the absence or a decrease from baseline in the amplitude of a valid measure of breathing during sleep that either reaches >50% with an oxygen desaturation of 3% or an arousal (alternatively, a 30% reduction with 4% desaturation). These definitions are recommended by the American

Key points

- OSAS refers to the presence of apnoeas/hypopnoeas together with related symptoms.
- Obstructive events are due to passive collapse of the upper airway at the end of expiration.
- Tissue pressure that causes this collapse is referred to as critical closing pressure (P_{crit}).
- Unstable breathing patterns that prolong expiratory time may promote this passive collapse of the upper airway.
- CPAP remains the treatment of choice since it counteracts P_{crit} and stabilises the breathing pattern.
- Alternative treatment methods mostly focus on the increase of the upper airway volume at the end of inspiration, since this lowers the P_{crit}.

Academy of Sleep Medicine (AASM). The Task Force of the AASM also states that there are common pathogenic mechanisms for obstructive apnoea syndrome, central apnoea syndrome, sleep hypoventilation syndrome and Cheyne–Stokes breathing. It was preferred to discuss them separately, although they could be placed under the common term of 'sleep-disordered breathing syndrome'. The definition of OSAHS using two components, daytime symptoms and breathing pattern disturbances during sleep, may suggest that there is a tight correlation between both. However, unfortunately, this is not the case. The breathing pattern abnormalities, mostly described by an AHI, only weakly correlate with quantified measures of sleepiness such as the Epworth Sleepiness Scale (ESS). This probably means that interindividual sensitivity, with some individuals coping better with sleep fragmentations then others, compromises the relationship between the AHI and scores of daytime sleepiness. In addition, epidemiological studies do show a wide spread in sleepiness in the general population. Obviously, epidemiological studies looking at the prevalence of OSAHS are all biased by the lack of a uniform definition. The prevalence of an AHI of >5 events per h in a general population (without taking into account symptoms of sleepiness) was previously estimated to be 24% in a male population. When symptoms of sleepiness were also taken into account, the prevalence decreased to 4% in men and 2% in women.

Assessment of OSAHS

Most widely used as gold standard for diagnosis is overnight polysomnography including nasal and/or oral airflow, thoracoabdominal movement, snoring, electroencephalography, electro-oculography, electromyography and oxygen saturation. Cardiorespiratory monitoring alone can be considered as highly sensitive (78–100%) and specific (67–100%). Sleepiness is often evaluated using the ESS, which assesses the global level of sleepiness and is independent of short-term variations in sleepiness. The ESS discriminates between normal and pathological sleepiness.

Pathophysiology

Structural narrowing of the upper airway is unlikely to be a major cause, since only weak correlations are found between the upper airway size in wakefulness and the AHI indices. Moreover, recent studies have shown that the upper airway collapse is not restricted to one place but rather a dynamic phenomenon starting at a certain level and spreading caudally. Upper airway obstruction involves more than one specific site of the upper airway in most sleep apnoea patients. The upper airway can collapse when insufficient load compensation can be generated when an imbalance between activation of the upper airway dilator muscles and the diaphragm occurs. When this occurs, the airway will collapse during inspiration or at least narrow with the development of flow limitation. There is, however, increasing evidence that the collapse of the upper airway occurs during expiration. Moreover, it has been convincingly shown that the upper airway behaves as a Starling resistor, making the collapse independent of the suction force brought about by the diaphragm, but dependent on the balance between upper airway pressure and the tissue pressure at the collapsible site. The airway remains patent, regardless of excessive pressure applied, as long as the critical closing pressure (P_{crit}) remains low relative to the pressure upstream of the collapsible segment (P_{u}). Closure of the upper airway occurs when P_{u} falls below the surrounding tissue pressure (P_{crit}). In the model of the Starling resistor, flow (V'_{max}) becomes a function of the pressure gradient and the resistance in the segment upstream to the collapsible segment (R_u):

$$V'_{max} = \frac{P_u - P_{crit}}{R_u} \quad (1)$$

The collapse of the upper airway then finally occurs during expiration when, due to the absence of dilator muscle, P_{crit} exceeds the upstream pressures. Prolonged expiratory time, as occurs during central apnoeas, therefore predisposes to collapse, but other factors may contribute and can be considered as risks. Therefore, central and obstructive events are closely linked. Sometimes, a central event with already partially collapsed upper airway can transit towards an obstructive event with ongoing occlusion of the upper airway despite the resumption of effort. Often, however, with resumption of effort at the end of the central apnoea, the obstruction of the upper airway disappears, presumably due to reactivation of the upper airway dilator muscles. The mechanisms remain, however, unclear and more research is needed to understand why central apnoeas sometimes are followed by obstructive ones and sometimes are followed by reopening of the airways. In any case, since central apnoeas can trigger classical obstructive apnoeas, the mechanisms leading to unstable breathing (and thus central apnoeas) are also important in the genesis of obstructive apnoeas.

Consequences

Cardiovascular consequences

Obstructive apnoea may generate negative intrathoracic pressure that increases left ventricular transmural pressure and left ventricular afterload. The negative pressure also draws more blood into the thorax and increases right ventricular preload. Intermittent hypoxia related to OSA will also impair cardiac contractility and diastolic relaxation (figure 1). OSA patients also have attenuated endothelium-dependent vasodilation and decreased circulating markers of nitric oxide. These effects, together

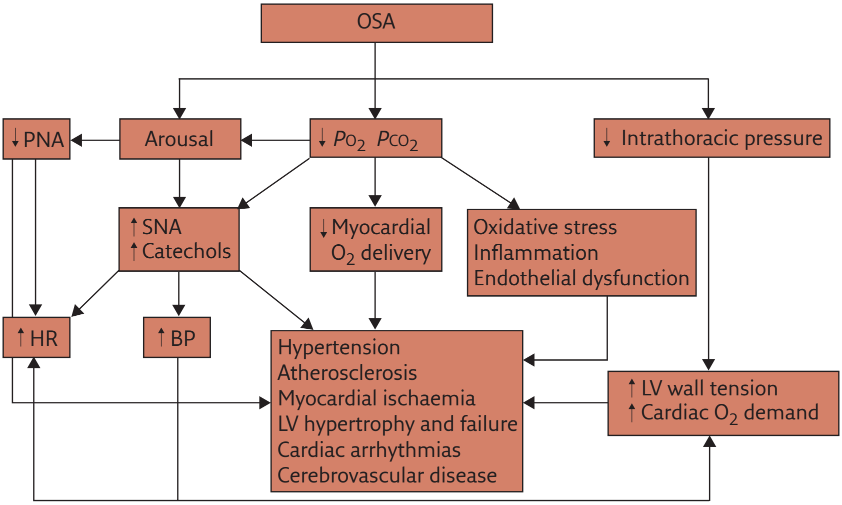

OSA
↓PNA
Arousal
↓ P_{O_2} P_{CO_2}
↓ Intrathoracic pressure
↑SNA
↑Catechols
↓Myocardial O_2 delivery
Oxidative stress
Inflammation
Endothelial dysfunction
↑HR
↑BP
Hypertension
Atherosclerosis
Myocardial ischaemia
LV hypertrophy and failure
Cardiac arrhythmias
Cerebrovascular disease
↑LV wall tension
↑Cardiac O_2 demand

Figure 1. Cardiovascular consequences of OSA. PNA: parasympathetic nerve activity; P_{O_2}: oxygen tension; P_{CO_2}: carbon dioxide tension; SNA: sympathetic nerve activity; HR: heart rate; BP: blood pressure; LV: left ventricular. Reproduced and modified from Bradley et al. (2009) with permission from the publisher.

with increased sympathetic vasoconstrictor activity and inflammation, will predispose to hypertension and atherosclerosis. In addition, platelet activation and aggregability are increased and predispose to thrombotic disease. Epidemiological studies indicate that OSA can initiate or promote cardiovascular disease such as hypertension, coronary heart disease, HF, cardiac arrhythmias (bradyarrhythmias, atrial fibrillation and ventricular ectopy) and cerebrovascular disease.

Metabolic consequences

OSA is associated with several components of the metabolic syndrome, mainly insulin resistance and abnormal lipid metabolism. Sleep restriction causes insulin resistance by inducing a pro-inflammatory state (increased release of interleukin-6 and tumour necrosis factor (TNF)-α). Epidemiological studies have shown that sleep-related hypoxaemia is associated with glucose intolerance independent of age, sex, BMI and waist circumference. The metabolic syndrome (for definitions, see Lévy *et al.* (2009)) can be triggered by both intermittent hypoxia and sleep fragmentation/deprivation. The mechanisms are given in figure 2. The metabolic syndrome can be due to the release of free fatty acids, angiotensin II and adipokines by adipose tissue, which may damage the pancreas, leading to insufficient insulin release and apparent insulin resistance. Mean and nadir S_{aO_2} during sleep are independent predictors of the metabolic syndrome in overweight children and adolescents.

CPAP treatment

Therapy with nasal CPAP: mode of action

Treatment with nasal CPAP (nCPAP) is perceived by most physicians as a very effective treatment for sleep apnoea and has been shown to be effective in controlled studies. nCPAP resulted in better sleep quality with a lower arousal index, less stage 1, and more stage 3 and 4 sleep in a placebo (using placebo capsules) controlled study. In addition, in milder forms of sleep apnoea, nCPAP improved self-reported symptoms of OSA, including snoring, restless sleep, daytime sleepiness and irritability. Neuropsychological test results also improve after nCPAP when compared to ineffective nCPAP. In addition, blood pressure can be reduced with nCPAP when

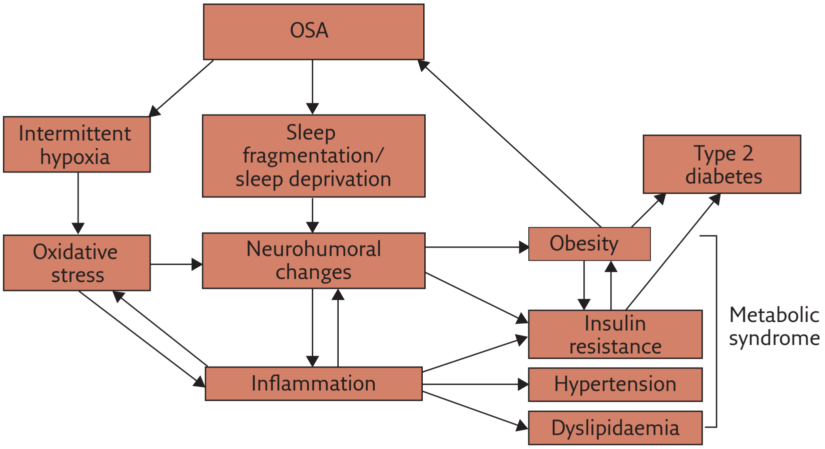


Figure 2. Mechanisms linking OSA and the metabolic syndrome. Reproduced and modified from Tasali et al. (2008) with permission from the publisher.

compared to oral placebo, especially in those patients using nCPAP for ≥3.5 h per night and in those with >20 4% desaturations per hour.

nCPAP and the upper airway

The occlusion of the upper airway can be prevented when either R_u or P_{crit} can be lowered. Regardless of the severity of the changes in P_{crit} and P_u, nCPAP can effectively increase (or restore) flow, largely through its effect on P_u (equation 1). Appropriate titrating of the CPAP pressure restores flow. nCPAP can increase P_u much more than local interventions like uvulopalatopharyngoplasty (UPPP) can do. It also explains, therefore, why nCPAP is, overall, much more clinically effective, as proven in controlled studies.

nCPAP and control of breathing

As indicated earlier, some clinical observations initially indicated that unstable breathing is part of OSAS, while more recent systematic analysis confirmed the increased loop gain and instability in the breathing pattern of OSA patients. It can be questioned therefore whether nCPAP can influence the control of breathing in (obstructive) sleep apnoea patients. One could demonstrate that prolonged treatment with nCPAP significantly decreases the slope of the hypercapnic ventilatory response curve when measured during wakefulness, together with an increase in P_{aO_2} and a decrease in the alveolar–arterial oxygen difference. All of these changes may contribute to lowering the gain in the system and promoting a more stable breathing pattern. Changes in lung volume, although mostly small, can also be observed during nCPAP therapy.

nCPAP has been demonstrated to be effective in central sleep apnoea as well. nCPAP can raise carbon dioxide tension above the apnoeic threshold and therefore eliminate central apnoeas. However, since as pointed out earlier, central apnoeas are also often characterised by (near) occlusion of the upper airway, nCPAP can presumably also be effective be preventing this collapse and its associated local reflexes.

nCPAP and the heart

nCPAP can effectively be used to treat acute cardiogenic pulmonary oedema with shifting volume from intra- to extrathoracic compartments.

nCPAP may relieve CSA in CHF patients by raising P_{aCO_2} above the apnoeic threshold. nCPAP may reduce ventilation by redistributing excess lung water to extrathoracic compartments, thereby reducing stimulation of pulmonary vagal irritant receptors. nCPAP may also unload the inspiratory muscles by increasing lung compliance again due to extrathoracic redistribution of lung water.

nCPAP may significantly reduce left ventricular afterload by lowering the transmural pressure in patients with compromised cardiac function. In the normal heart, where cardiac output is largely preload dependent, CPAP decreases cardiac output by reducing left ventricular preload. The failing heart, by contrast, is relatively insensitive to changes in preload but very sensitive to reductions in afterload. CPAP-induced reductions in left ventricular transmural pressure (and afterload) can augment cardiac output.

nCPAP may also attenuate sympathetic nervous activity and increase cardiac vagal modulation of the heart with favourable effects on blood pressure regulation.

In a large prospective study, severe untreated OSA patients had more fatal and nonfatal cardiovascular events. This difference disappeared with nCPAP treatment.

nCPAP and metabolic/systemic effects of OSA

nCPAP may improve the metabolic syndrome although it is not always certain that nCPAP has an independent effect. nCPAP also lowers TNF-α, interleukin-6 and C-reactive protein.

Non-CPAP Treatment

Mandibular advancement devices

Mandicular advancement devices (MADs) are the most common oral appliances used for the treatment of OSA and/or snoring. They have either a one-piece (monobloc) or two-piece (duobloc) configuration, while customised devices have a better retention, tolerance and efficacy. MADs are effective if they increase the volume of the upper airway, which may enlarge at some sites and narrow at others. The overall efficacy, therefore, is sometimes suboptimal; 65% of patients achieve a 50% reduction in AHI. In addition, snoring, excessive daytime sleepiness, neuropsychological function and cardiovascular risk may decrease. It is important to try to predict the outcome. Imaging and modelling studies can be of help for this purpose.

Surgical treatment

Several techniques have been performed, all with the aim to enlarge the volume of the upper airway and to reduce the closing pressure. UPPP reduces upper airway obstruction by shortening the uvula, trimming the soft palate, and suturing back the anterior and posterior pharyngeal pillars. Tonsillectomy is performed at the same time if the tonsils are found to be enlarged. Maxillomandibular advancement osteotomy advances the maxilla and mandible to enlarge the retrolingual and retropalatal spaces. Adenotonsillectomy is the first-line treatment in children. Electrical stimulation of the genioglossus with an implanted pacemaker has recently been tested and found to be efficient in selected patients, although more clinical studies are needed in order to learn which patients will benefit most. Recently, clinical studies have indicated that prediction of outcome is worthwhile. The effect of tonsillectomy in patients with Down syndrome can be predicted using advanced imaging techniques. In addition, the result of hypoglossal stimulation is dependent on pre-existing upper airway anatomy that can be described using several imaging techniques. It seems therefore likely that the field will evolve, probably very soon, toward personalised medicine approaches, where invasive and irreversible treatment strategies will be preceded by predictive diagnostic approaches.

References

- American Academy of Sleep Medicine Task Force (1999). Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep*; 22: 667–689.
- Bradley TD, *et al.* (2009). Obstructive sleep apnoea and its cardiovascular consequences. *Lancet*; 373: 82–93.
- Chan AS, *et al.* (2008). Non-positive airway pressure modalities: mandibular advancement devices/positional therapy. *Proc Am Thorac Soc*; 5: 179–184.
- De Backer JW, *et al.* (2008). Novel imaging techniques using computer methods for the evaluation of the upper airway in patients with sleep-disordered breathing: a comprehensive review. *Sleep Med Rev*; 12: 437–447.
- Halle TR, *et al.* (2017). Surgical treatment of OSA on cardiovascular outcomes: a systematic review. *Chest*; 152: 1214–1229.

- Jennum P, *et al.* (2009). Epidemiology of sleep apnoea/hypopnoea syndrome and sleep-disordered breathing. *Eur Respir J*; 33: 907–914.
- Lévy P, *et al.* (2009). Sleep, sleep-disordered breathing and metabolic consequences. *Eur Respir J*; 34: 243–260.
- Marin JM, *et al.* (2005). Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*; 365: 1046–1053.
- McArdle N, *et al.* (2001). Effect of continuous positive airway pressure on sleep architecture in the sleep apnea-hypopnea syndrome: a randomized controlled trial. *Am J Respir Crit Care Med*; 164: 1459–1463.
- Schwab RJ, *et al.* (2017). Digital morphometrics: a new upper airway phenotyping paradigm in OSA. *Chest*; 152: 330–342.
- Schwab RJ, *et al.* (2018). Anatomic predictors of response and mechanism of action of upper airway stimulation therapy in patients with obstructive sleep apnea. *Sleep*; 41: https://doi.org/10.1093/sleep/zsy021.
- Slaats M, *et al.* (2017). Predicting the effect of treatment in paediatric OSA by clinical examination and functional respiratory imaging. *Pediatr Pulmonol*; 52: 799–805.
- Slaats MA, *et al.* (2015). Upper airway imaging in pediatric obstructive sleep apnea syndrome. *Sleep Med Rev*; 21: 59–71.
- Slaats MALJ, *et al.* (2018). The role of functional respiratory imaging in treatment selection of children with obstructive sleep apnea and Down syndrome. *J Clin Sleep Med*; 14: 651–659.
- Tasali E, *et al.* (2008). Obstructive sleep apnea and metabolic syndrome: alterations in glucose metabolism and inflammation. *Proc Am Thorac Soc*; 5: 207–217.
- Vanderveken OM, *et al.* (2008). Comparison of a custom-made and a thermoplastic oral appliance for the treatment of mild sleep apnea. *Am J Respir Crit Care Med*; 178: 197–202.
- Verbraecken JA, *et al.* (2009). Upper airway mechanics. *Respiration*; 78: 121–133.
- Verhulst SL, *et al.* (2007). Sleep-disordered breathing and the metabolic syndrome in overweight and obese children and adolescents. *J Pediatr*; 150: 608–612.
- Won CH, *et al.* (2008). Surgical treatment of obstructive sleep apnea: upper airway and maxillomandibular surgery. *Proc Am Thorac Soc*; 5: 193–199.
- Younes M, *et al.* (2007). Mechanisms of breathing instability in patients with obstructive sleep apnea. *J Appl Physiol* (1985); 103: 1929–1941.
- Young T, *et al.* (1993). The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*; 328: 1230–1235.

Central sleep apnoea

Konrad E. Bloch and Thomas Brack

Central sleep apnoea/hypopnoea refers to the cessation or reduction of ventilation lasting for ≥10 s (in adults) due to a transient loss of neural output to the respiratory muscles. Many patients with central sleep apnoea (CSA) have mild hypocapnia or normocapnia but hypercapnia is less common, although hypoventilation may also accompany CSA. A periodic pattern of waxing and waning of ventilation with periods of hyperventilation alternating with central apnoea/hypopnoea is termed Cheyne–Stokes respiration (CSR).

Prevalence, aetiology and pathophysiology

The prevalence of CSA in the general population is not known. However, it seems to be significantly less common than OSA, as <5% of patients referred to a sleep laboratory reveal predominant CSA. In contrast, a relatively high prevalence of CSA is observed in association with various conditions including CHF, pulmonary hypertension, ischaemic stroke, neuromuscular disease, obesity hypoventilation syndrome and opioid use, or during initiation of CPAP therapy in certain patients with OSA. In healthy subjects, CSA may occur during hypoxia at altitude. Idiopathic CSA, by definition, is not associated with any comorbid condition.

Pathophysiological mechanisms underlying CSA include:

- respiratory control instability, due to an increased chemical drive, so that the prevailing P_{aCO_2} is close to the apnoea threshold
- a prolonged circulation time
- altered respiratory mechanics

Subsequently, different forms of CSA will be discussed.

Key points

- Central sleep apnoea (CSA) signifies the loss or reduction in ventilation due to a transient loss of neural output to the respiratory muscles.
- A high prevalence of CSA is observed in association with conditions such as CHF, pulmonary hypertension, cerebral stroke, neuromuscular disease, obesity hypoventilation syndrome and opioid use.
- Risk factors for CSA/Cheyne–Stokes respiration are age >60 years, male sex, severe HF, hypocapnia and atrial fibrillation.
- Treatment includes oxygen, acetazolamide and positive pressure ventilation.

CSR/CSA syndrome in CHF patients

Left-heart failure that increases pulmonary venous pressure is regarded as a source of CSR, as pulmonary congestion stimulates stretch receptors that sensitise the peripheral chemoreceptors to carbon dioxide through vagal afferents. The increased ventilatory sensitivity to carbon dioxide drives the $P_{\mathrm{aCO_2}}$ closer to the apnoea threshold, thereby promoting the susceptibility to central apnoea. Moreover, hypoxia that follows apnoea/hypopnoea enhances post-apnoeic hyperventilation. If chemical control prevails over cortical influences on the respiratory controller, as typically occurs during sleep, patients develop an oscillatory breathing pattern that causes sympathetic overstimulation in patients who are already sympathetically stimulated through their heart failure.

Among patients with moderate to severe HF (left ventricular ejection fraction (LVEF) ≤55%), the prevalence of sleep apnoea (both obstructive and central) is very high irrespective of the clinical suspicion (figure 1).

Criteria for CSR/CSA have not been uniformly accepted. According to the American Academy of Sleep Medicine, CSR should be scored if at least three successive cycles of cyclic crescendo–decrescendo changes in breathing amplitude are present for ≥10 consecutive minutes or when a central AHI >5 events·h^{-1} arises. In the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) trial, a large multicentre study that evaluated the effectiveness of CPAP therapy in patients with HF and CSA, inclusion criteria required ≥15 apnoeas/hypopnoeas per hour with >50% central events and a LVEF <40%. Obviously, the AHI threshold used to define the presence of CSR has a major impact on prevalence estimates (figure 1).

In some patients, CSR/CSA and OSA may coexist and alternate over the course of a night. Symptoms attributable to CSR/CSA are not well defined but may include paroxysmal nocturnal dyspnoea, poor sleep quality, excessive daytime sleepiness, fatigue and poor exercise tolerance.

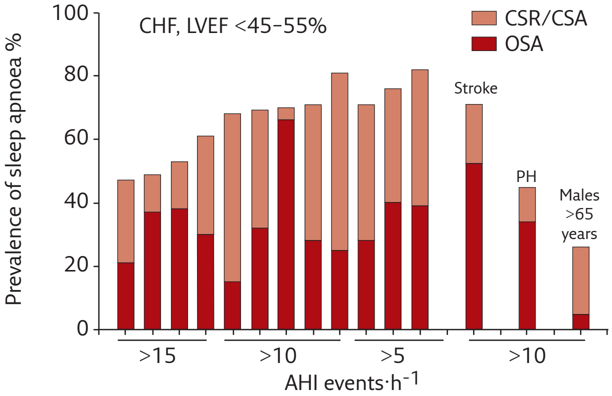


Figure 1. The prevalence of OSA and CSA/CSR in patients with CHF is very high (47–82%), depending on the severity of HF and on the cut-off level of the AHI. Sleep apnoea is also common in patients with stroke or pulmonary hypertension (PH). The columns represent the prevalence of sleep apnoea observed in different studies in patients with various conditions. For comparison, data from a community sample of males aged >65 years are also shown. Reproduced and modified from Brack et al. *(2012) with permission from the publisher.*

CSR/CSA in heart failure patients is associated with poor prognosis. Several studies have found an increased mortality in patients with CSR/CSA even after controlling for the severity of HF, age, sex and other potential confounders. Mortality was particularly high in patients presenting with daytime CSR during physical activity (figure 2).

Sleep-related breathing disturbances should be suspected in all patients with HF who suffer from nocturnal dyspnoea, unrefreshing sleep or daytime sleepiness. Particular risk factors for CSA/CSR include:

- severe HF
- older age (≥60 years)
- male sex
- hypocapnia
- atrial fibrillation
- CSR observed during the day

The diagnosis should be evaluated by polysomnography or a cardiorespiratory sleep study, as pulse oximetry cannot make the important distinction between CSA and OSA.

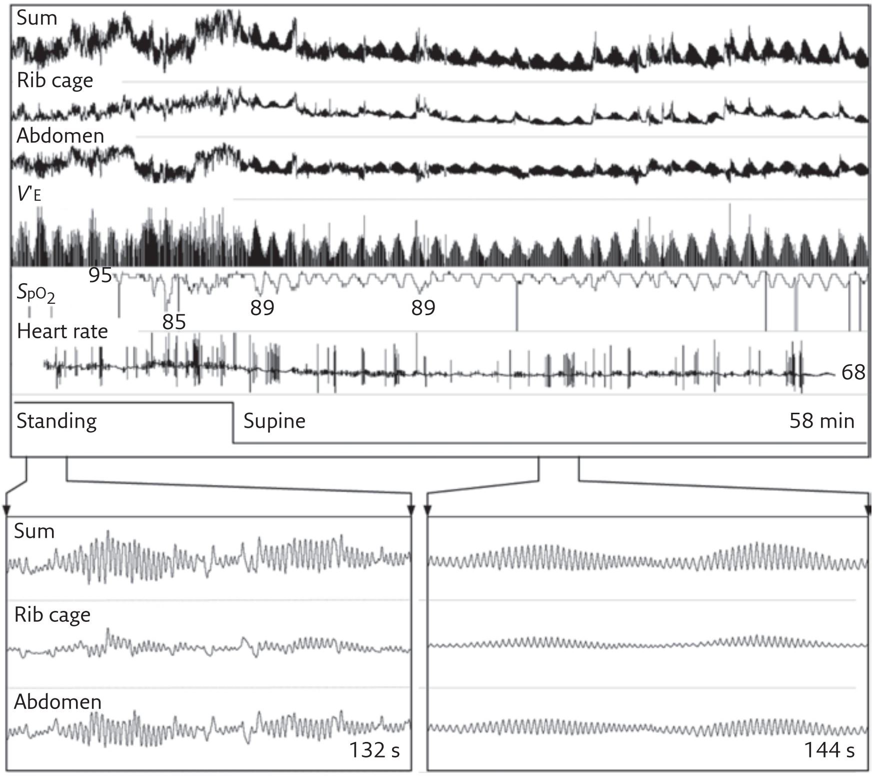


Figure 2. CSR in a patient with CHF. Inductive plethysmographic signals from rib cage and abdominal sensors showing regular waxing and waning of ventilation with central hypopnoeas and corresponding oscillations of oxygen saturation. The upper panel represents a 58-min daytime recording, the lower panels show enlarged portions obtained while standing (left) and in the supine position (right). Reproduced and modified from Brack et al. *(2007) with permission from the publisher.*

Optimised medical therapy of HF is the first step in the treatment of CSR/CSA. Cardiac resynchronisation by biventricular pacing and heart transplantation may also alleviate CSR/CSA. If medical therapy alone is ineffective, NIV may be required. Nocturnal CPAP has been shown to improve nocturnal CSR/CSA, oxygen saturation, LVEF, sympathetic nervous system activity and 6-min walking distance. These effects are thought to be mediated by the increase in intrathoracic pressure induced by CPAP, which reduces both afterload and preload by decreasing transmural ventricular pressure and venous return so that cardiac function improves in patients with increased filling pressures. Additionally, CPAP stabilises CSR by raising the end-expiratory lung volume. Despite its positive effects on several outcomes described above, CPAP did not prolong survival without heart transplantation during a 2-year follow-up in a large trial (CANPAP). Yet, a *post hoc* analysis suggested a survival benefit in a subgroup of patients in whom CPAP sufficiently suppressed CSR/CSA. Adaptive servoventilation (ASV) is a mode of bilevel positive airway pressure ventilation that continuously adjusts pressure support according to the breathing pattern of the patient in order to stabilise periodic breathing (figure 3). It is a treatment option for CSR/CSA as it has been shown to improve nocturnal breathing pattern, daytime vigilance and quality of life after treatment for several weeks. Despite the potential of ASV to reverse CSR, ASV did not improve survival in patients with CSR due to severe CHF in a recent randomised controlled trial. The trial (SERVE-HF) included 1325 patients with a LVEF of ≤45% (mean 32±8%) who were followed an average of 31 months; all-cause mortality was defined as a primary end-point and cardiovascular death as a secondary end-point. Patients treated with ASV had a higher incidence of cardiac death compared to patients receiving standard care (25% *versus* 20%, respectively; p=0.03). Thus, currently, ASV should not be used for the treatment of CSA-predominant sleep disordered breathing in adults with CHF and an ejection fraction ≤45%. Acetazolamide and theophylline have both reduced CSR/CSA in some studies but these drugs are currently not generally recommended because of limited data on their effectiveness and potential adverse effects. Supplemental nocturnal oxygen has provided inconsistent results, with some studies showing a reduction in CSR/CSA along with improvements in physical performance or quality of life, while others failed to reproduce these benefits. Further studies are required to better define the role of these adjuncts for the treatment of heart failure in patients with CSR/CSA.

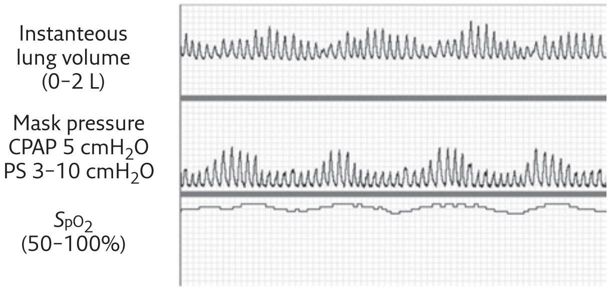


Figure 3. Recordings of instantaneous lung volume by respiratory inductive plethysmography and mask pressure during ASV in a patient with HF. In this mode of pressure support (PS) ventilation, the inspiratory pressure support is increased during hypopnoeic or apnoeic phases of CSR whereas PS is reduced to a minimal level during hyperpnoeic phases.

Treatment-emergent CSA

In some patients diagnosed with OSA, a CSR/CSA breathing pattern may emerge during initial CPAP therapy. The clinical relevance of this phenomenon, referred to as treatment-emergent CSA, is still a matter of debate, as studies suggest that CSA disappears in the majority of OSA patients during prolonged CPAP therapy. However, persistent residual CSA may disturb sleep quality, prevent complete symptomatic improvement and may lead to CPAP intolerance in OSA patients. In patients with treatment-emergent CSA, ASV has been successfully used to normalise the breathing pattern and improve sleep quality.

Idiopathic CSA syndrome

Idiopathic CSA syndrome (figure 4) is, by definition, not associated with any underlying disease. CSA causes sleep fragmentation, which may be perceived as unrefreshing sleep and result in daytime sleepiness. Idiopathic CSA is thought to be much less common than OSA, although no systematic epidemiological studies have been performed. Treatment options include acetazolamide, theophylline, CPAP and ASV.

CSA in various conditions

CSA and ataxic breathing have been observed in patients on chronic opioid medication, and can be successfully treated with ASV, although the relevance of the breathing disturbances requires further study. Patients with preceding stroke or neuromuscular disease, such as post-polio syndrome, motor neuron disease or multiple system atrophy, or with idiopathic central hypoventilation may exhibit CSA with or without associated OSA and/or hypoventilation. Depending on the prevailing breathing disturbance, bilevel positive pressure ventilation, CPAP or ASV may improve breathing and alleviate symptoms.

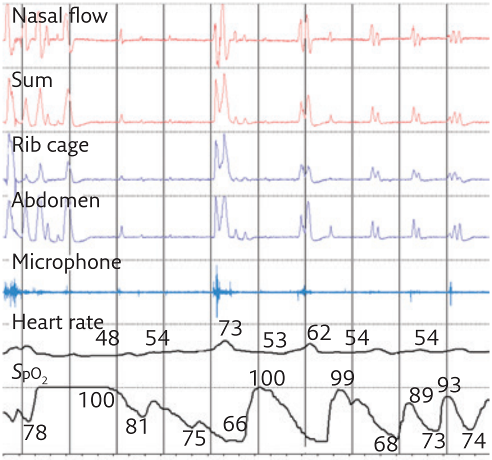


Figure 4. Idiopathic CSA in a 56-year-old male suffering from unrefreshing sleep. The 5-min recording shows repetitive central apnoeas of variable duration (20–90 s) associated with severe oxygen desaturation (minimal value of 66%). The absence of excursions in the inductive plethysmographic rib cage and abdominal signals during cessation of airflow indicates that apnoeas are due to intermittent loss of respiratory muscle activity.

High-altitude periodic breathing

In healthy subjects, hypobaric hypoxia at altitudes of >1600 m may induce periodic breathing with central apnoea/hypopnoea. Breathing instability is related to an enhanced chemosensitivity (high controller gain) causing a tendency for a ventilatory overshoot and hyperventilation with a reduced carbon dioxide reserve, *i.e.* the eupnoeic carbon dioxide tension approaches the apnoeic threshold, which promotes apnoea during minor ventilatory alterations. Symptoms may include paroxysmal dyspnoea and poor sleep quality. In some subjects, high-altitude periodic breathing is associated with acute mountain sickness, a syndrome characterised by headaches, insomnia, poor appetite, fatigue and, in more severe forms, ataxia and altered consciousness. The diagnosis of high-altitude periodic breathing is based on clinical observations in the appropriate context combined with pulse oximetry or more sophisticated sleep studies. Treatment is often not required but can be performed by altitude descent, or the administration of supplemental oxygen or acetazolamide, which is also effective against acute mountain sickness.

Conclusion

CSA/CSR is less common than OSA. However, in certain conditions, including CHF, neuromuscular disorders, opioid use and high altitude, the prevalence of CSA is high. Treatment for CSA is not as well established as that for OSA, and it may include oxygen, acetazolamide and positive pressure ventilation.

Further reading

- Aurora N, *et al.* (2012). The treatment of central sleep apnoea syndromes in adults: Practice parameters with an evidence-based literature review and meta-analyses. *Sleep*; 35: 17–40.
- Brack T, *et al.* (2007). Daytime Cheyne–Stokes respiration in ambulatory patients with severe congestive heart failure is associated with increased mortality. *Chest*; 132: 1463–1471.
- Brack T, *et al.* (2012). Cheyne–Stokes respiration in patients with heart failure: Prevalence, causes, consequences and treatments. *Respiration*; 83: 165–176.
- Bradley DT, *et al.* (2005). Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med*; 353: 2025–2033.
- Cowie MR, *et al.* (2015). Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med*; 373: 1095–1105.
- Dai Y, *et al.* (2008). Central sleep apnea and Cheyne–Stokes respiration. *Proc Am Thorac Soc*; 5: 226–236.
- Eckert DJ, *et al.* (2007). Central sleep apnea. *Chest*; 131: 595–607.
- Javaheri S, *et al.* (2009). The prevalence and natural history of complex sleep apnea. *J Clin Sleep Med*; 5: 205–211.
- Randerath W, *et al.* (2017). Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. *Eur Respir J*; 49: 1600959.
- Strohl KP. Patient education: Sleep apnea in adults (Beyond the Basics). www.uptodate.com/contents/sleep-apnea-in-adults-beyond-the-basics?
- Walker JM, *et al.* (2007). Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. *J Clin Sleep Med*; 3: 455–461.

Hypoventilation syndromes

Andrea Aliverti

Sleep-related hypoventilation syndromes, together with central and obstructive sleep apnoea syndromes, are a part of so-called sleep-related breathing disorders (table 1).

Sleep-induced hypoventilation is characterised by elevated levels of P_{aCO_2} of >45 mmHg (5.99 kPa) while asleep or disproportionately increased relative to levels during wakefulness.

Pathophysiology

Nocturnal hypoventilation can be attributed to respiratory pump failure in relation to decreased ventilatory drive (won't breathe), which may be due to respiratory dysfunction secondary to polio sequelae, central hypoventilation, amyotrophic lateral sclerosis, Arnold–Chiari malformation or the following: respiratory centres depression (hypnotics); alteration of respiratory nerve conduction (Guillain–Barré syndrome); transmission to the respiratory muscles (myasthenia) or worsening mechanics (can't breathe) with respiratory muscle alteration (muscular dystrophy), chest wall deformities or severe obesity. In the latter situations, lungs are normal and associated hypoxaemia is due to the displacement of oxygen in the alveoli from increasing carbon dioxide levels, as predicted by the alveolar air equation. If the lungs are abnormal

Key points

- Sleep-induced hypoventilation is characterised by increased P_{aCO_2} levels of >45 mmHg (5.99 kPa).
- Nocturnal hypoventilation is associated with decreased ventilator drive, respiratory iatrogenic depression, alteration of respiratory nerve conductance, muscular disease, chest wall deformities or severe obesity.
- Obesity hypoventilation syndrome (OHS) is the association of obesity and sleep disordered breathing with daytime hypersomnolence and hypercapnia in the absence of other respiratory diseases.
- Nowadays, OHS is the most common sleep-related hypoventilation syndrome.
- Nocturnal polygraphy evaluation is needed in order to diagnose OHS.
- In OHS, NIV is used as the first-line treatment with supplementary oxygen when P_{aCO_2} ≥50 mmHg (6.65 kPa); if P_{aCO_2} <50 mmHg, nasal CPAP plus oxygen may be discussed as a first-line treatment after a night trial of nasal CPAP plus oxygen.

Table 1. Conditions of hypoventilation syndromes

Presence of an extra-/intrapulmonary restrictive disorder

- OHS
- Neuromuscular diseases
  - Duchenne muscular dystrophy, Steinert myotony, polio sequelae, amyotrophic lateral sclerosis, high spinal injuries with tetraplegia and respiratory paralysis (less frequent are acid maltase deficiency and spinal muscular atrophy)
- Chest wall diseases
  - Kyphoscoliosis and/or TB sequelae
- Other conditions
  - Respiratory centres depressant drugs
  - Neurologic conditions: Arnold–Chiari malformations, brainstem tumours, space occupying lesions, vascular malformations, central nervous system infection, stroke and neurosurgical procedure which may be associated with central hypoventilation
  - Congenital central hypoventilation

Presence of an obstructive disorder

- COPD, diffuse bronchiectasis and CF are the most frequent conditions

(COPD, tuberculous sequelae, CF or diffuse bronchiectasis), hypercapnia is mainly due to worsening mechanics and ventilation–perfusion inequalities.

During the night, ventilatory response to hypoxaemia and hypercapnia is largely reduced during rapid eye movement (REM) sleep with dysrhythmic breathing and less reduced during non-REM sleep. The result is a reduction of alveolar ventilation by altering V'_E and/or dead space volume/tidal volume.

Respiratory mechanics change during sleep and thereby worsen gas exchange, particularly in neuromuscular diseases and obstructive airways diseases. REM sleep induces skeletal muscle hypotonia sparing the diaphragm and not the accessory respiratory muscles, with deleterious effects in conditions for which these muscles are necessary to maintain normal ventilation.

REM sleep also alters upper airways patency and reduces chronic respiratory failure.

Clinical features

Hypoventilation *per se* generates a clinical syndrome associated with, in typical cases, dyspnoea during activities of daily living in the absence of paralysis, poor sleep quality, excessive daytime fatigue and sleepiness, nocturnal or early morning headache, cyanosis and evidence of right heart failure.

Diagnosis

The presence of such symptoms highlights the need to perform a physical examination, pulmonary function tests and a chest radiograph, as well as measurement of arterial blood gases in the awake and asleep patient, *i.e.* S_{aO_2} and P_{tCO_2}. The results of this initial investigation are concluded by full night ventilatory polygraphy (respiratory signals only) or polysomnography (respiratory and neurological signals; electroencephalography, electrooculography, electromyography). Chronic daytime hypercapnia is associated with and preceded by sleep-related hypoventilation.

Aetiology

Presence of an extra-/intrapulmonary restrictive disorder

If obesity is present the most frequent diagnosis is obesity hypoventilation syndrome (OHS), previously called the 'Pickwickian syndrome'. The definition of OHS is daytime carbon dioxide tension >45 mmHg (5.99 kPa) and oxygen tension <70 mmHg (9.31 kPa), in the presence of BMI >30 $\text{kg}\cdot\text{m}^{-2}$ and sleep disordered breathing, and in the absence of another explanation for hypercapnia. The prevalence of OHS is increasing with global levels of obesity. The estimated prevalence is 0.3–0.4% in the general population and 10–20% in those with sleep disordered breathing. OHS is frequently unrecognised until acute or chronic ventilator decompensation develops.

The pathogenesis of OHS involves abnormal respiratory mechanics, namely decreased functional residual capacity and reduced respiratory system compliance, determining an increased work of breathing, in turn associated to high ventilator drive and increased respiratory muscle recruitment. In addition, the reduction of lung volume below the closing capacity determines small airways obstruction and consequently impairment of gas exchange and altered hypoxic and hypercapnic ventilator responses, linked, in part, to chronic hypoxaemia and poor sleep quality. The latter includes worsened nocturnal hypercapnia, nocturnal hypoxaemia and OSA. Hypothalamic dysfunction and hormonal influences also play a role in altering ventilatory control and chemoreceptor sensitisation. Obesity and OHS are associated with significantly higher leptin concentrations; however, with an impairment of the normal effects of leptin, implying the existence of a leptin-resistant state.

In order to establish a diagnosis of OHS, polysomnographic evaluation is needed and the ventilatory treatment needs to be adapted. The sleep respiratory pattern can present as obstructive apnoeas and hypopnoeas (90% of cases), obstructive hypoventilation due to increased upper airway resistance and/or central hypoventilation (10% of cases) (figure 1).

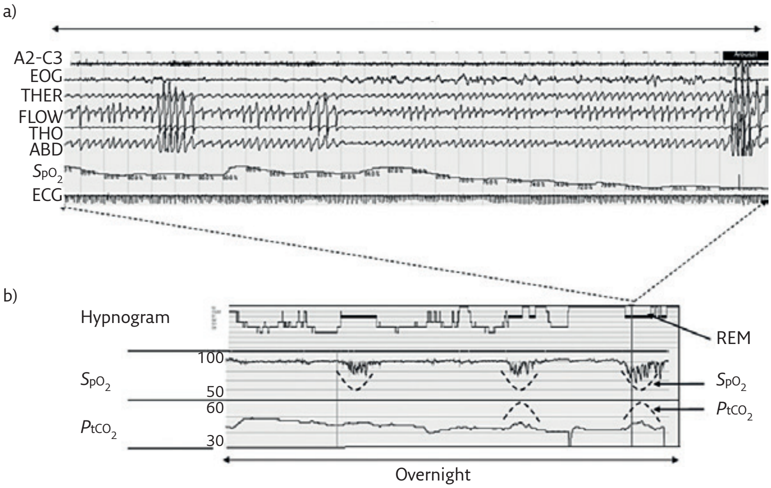


Figure 1. Polysomnographic pattern of REM sleep hypoventilation. a) 5-min epoch: sustained reduction in airflow amplitude concurrently to phasic REM sleep. A2–C3: electroencephalogram; ABD: abdominal movements; EOG: electro-occulogram; FLOW: nasal pressure; THER: bucconasal thermistor; THO: thoracic movements. b) Overnight hypnogram: see the increase in P_{tCO_2} *during REM sleep. Reproduced from Borel* et al. *(2012) with permission.*

Without adequate treatment, patients with OHS develop cor pulmonale, recurrent episodes of hypercapnic respiratory failure and loss of survival. OHS is one of the many aetiologies of chronic respiratory failure and has become a growing indication to initiate acute and/or long-term mechanical NIV. Mechanisms of action include resting of the respiratory muscles, an increase in thoracic compliance and resetting of the respiratory centres. In OHS, nocturnal mechanical NIV has been shown to be clinically effective because of a rapid and sustained improvement of daytime arterial blood gas levels and a net reduction of daytime sleepiness.

In OHS, mechanical NIV is associated with a significant improvement in arterial blood gases and decrease of hospital stays for cardiac and/or respiratory illness during the 3 years following the initiation of the treatment. NIV is cost-effective and improves morbidity and mortality in such patients. In patients with obesity-related chronic respiratory failure and severe OSAS, an initial CPAP trial conducted for a duration of 2–4 weeks is, however, recommended. An assessment of CPAP efficacy should, at least, include nocturnal oximetry integrated with $P_{\mathrm{tCO_2}}$ and respiratory polygraphy or polysomnography. In case of persisting sleep-related hypoventilation despite adequate CPAP therapy, shifting to NIV is justified (figure 2).

Medical management is mainly orientated towards weight loss. A reduction of 5–10% of body weight can result in a significant decrease in $P_{\mathrm{aCO_2}}$. Unfortunately, weight loss by diet alone is difficult to achieve and sustain; thus, bariatric surgery may be proposed in the youngest patients. After significant weight-reduction surgery, patients with OHS experience long-term improvement of arterial blood gases and dyspnoea, which may lead to discontinuation of the ventilator treatment after night ventilator polygraphy monitoring showing disappearance of sleep disordered breathing.

If obesity is absent or not predominant, the most frequent conditions are: neuromuscular diseases with Duchenne muscular dystrophy; Steinert myotony; polio sequelae; amyotrophic lateral sclerosis; and high spinal injuries with tetraplegia and respiratory paralysis (less frequent are acid maltase deficiency and spinal muscular atrophy), and chest wall diseases with kyphoscoliosis and/or TB sequelae.

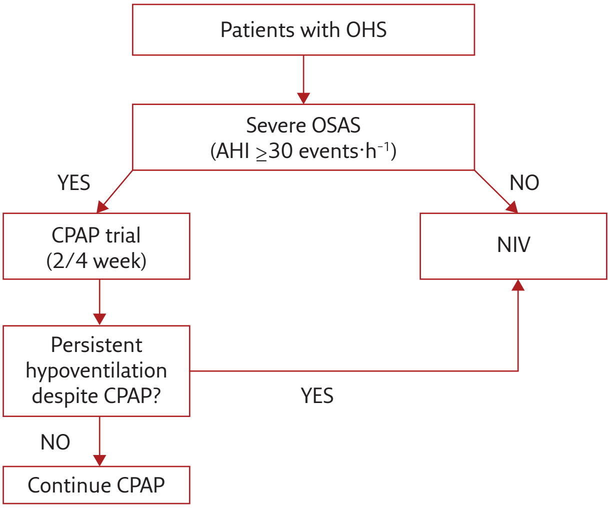


Figure 2. Algorithm for choosing the appropriate positive airway pressure therapy in patients with obesity-related hypoventilation in the clinical setting. Adapted from Borel et al. *(2018).*

Both inspiratory muscle weakness and scoliosis contribute to the restrictive ventilatory defect found in patients with neuromuscular disease. These diseases represent the best indication for the application of acute and chronic mechanical ventilation (mainly with NIV) and, in some severe situations or after failure of NIV, with invasive mechanical ventilation and tracheostomy. Differences in the pattern of sleep disordered breathing depend on respiratory and bulbar muscle involvement. Obstructive apnoea is frequently observed in younger Duchenne muscular dystrophy patients and associated with steroid therapy. With progressive diaphragm involvement, REM-related hypoventilation is present, evolving into persistent hypoventilation during non-REM and REM sleep once vital capacity falls below 40%. In those neuromuscular patients with preserved diaphragm function, like type 2 spinal muscle atrophy, mild hypoxaemia with minimal hypercapnia or normocapnia may be seen overnight. In patients with restrictive disorders due to neuromuscular disease or chest wall disorders, NIV is effective at controlling daytime arterial blood gas tensions, as it improves chemosensitivity and has a minimal effect on respiratory muscle strength.

Other conditions of sleep-related hypoventilation

There are less frequent conditions including neurological conditions such as Arnold–Chiari malformations, brainstem tumours, space occupying lesions, vascular malformations, central nervous system infection, stroke, or neurosurgical procedure which may be associated with central hypoventilation.

Congenital central hypoventilation syndrome is a rare disorder of ventilator control that typically presents in newborns and mainly results from a polyalanine repeat expansion mutation in the PHOX2B gene. It results in the failure of automatic central control of breathing in infants who do not breathe spontaneously or who breathe shallowly and erratically. Sufferers are generally treated by mechanical ventilation with tracheostomy and, in less severe situations, by mechanical NIV. Some rare conditions of proven sleep-related hypoventilation for which all the previous aetiologies have been ruled out are considered as idiopathic; it is always important to review the medications of such patient in order to detect intake of respiratory centres depressors (morphine, antitussive drugs, hypnotic and sedatives compounds) which are often used by elderly people.

Presence of an obstructive disorder

COPD, diffuse bronchiectasis and CF are the most frequent conditions. During sleep there is a worsening of awake hypoxaemia and hypercapnia, especially during REM sleep. Mechanical NIV is generally proposed after failure of long-term oxygen therapy in hypercapnic COPD when frequent episodes of acute respiratory decompensation occur and/or when baseline P_{aCO_2} progressively worsens. COPD patients with obesity must be investigated for possible overlap syndrome, which is associated with OSA and COPD and is frequently a good responder to mechanical NIV.

Further reading

- Bannerjee D, *et al.* (2007). Obesity hypoventilation syndrome: hypoxemia during CPAP. *Chest*; 131: 1678–1684.
- Borel JC, *et al.* (2012). Obesity hypoventilation syndrome: from sleep-disordered breathing to systemic comorbidities and the need to offer combined treatment strategies. *Respirology*; 17: 601–610.

- Borel JC, *et al.* (2018). Chronic ventilation in obese patients. *In:* Esquinas AM, *et al.*, eds. Mechanical ventilation in the critically ill obese patient. Cham, Springer; pp. 265–277.
- Casey KR, *et al.* (2007). Sleep related hypoventilation/hypoxemic syndromes. *Chest*; 131: 1936–1948.
- Chouri-Pontarollo N, *et al.* (2007). Impaired objective daytime vigilance in obesity-hypoventilation syndrome: impact of noninvasive ventilation. *Chest*; 131: 148–155.
- Cuvelier A, *et al.* (2007). Obesity hypoventilation syndrome. New insights in the Pickwick papers. *Chest*; 131: 7–8.
- de Lucas-Ramos P, *et al.* (2004). Benefits at 1 year of nocturnal intermittent positive pressure ventilation patients with obesity-hypoventilation syndrome. *Respir Med*; 98: 961–967.
- Guo YF, *et al.* (2007). Respiratory patterns during sleep in OHS patients treated with nocturnal pressure support. *Chest*; 131: 1090–1099.
- Kessler R, *et al.* (2001). The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. *Chest*; 120: 369–376.
- Masa JF, *et al.* (2015). Efficacy of different treatment alternatives for obesity hypoventilation syndrome. Pickwick study. *Am J Respir Crit Care Med*; 192: 86–95.
- Mokhlesi B (2007). Positive airway pressure titration in obesity hypoventilation syndrome. CPAP or bi-level AP? *Chest*; 131: 1624–1626.
- Mokhlesi B (2010). Obesity hypoventilation syndrome. A state of the art review. *Respir Care*; 55: 1347–1365.
- Muir JF, *et al.* (2008) . Management of chronic respiratory failure and obesity. *In:* Ambrosino N, *et al.*, eds. Ventilatory support for chronic respiratory failure. Vol. 1. New York, Informa Healthcare, pp. 433–444.
- Piper AJ, *et al.* (2011). Obesity hypoventilation syndrome: mechanism and management. *Am J Respir Crit Care Med*; 183: 292–298.
- Piper AJ, *et al.* (2014). Hypoventilation syndromes. *Compr Physiol*; 4: 1639–1676.
- Simonds AK (2013). Chronic hypoventilation and its management. *Eur Respir Rev*; 22: 325–332.

Respiratory failure

Nicolino Ambrosino and Fabio Guarracino

The respiratory system consists of two parts. The lung performs gas exchange and the pump ventilates the lung. The pump consists of the chest wall, including the respiratory muscles, and the respiratory controllers in the central nervous system (CNS) linked to respiratory muscles through spinal and peripheral nerves.

When respiratory failure ensues, the respiratory system fails in one or both of its gas exchange functions, *i.e.* oxygenation of mixed venous blood and/or elimination of carbon dioxide (figure 1).

The diagnosis of respiratory failure is not clinical but based on arterial gas assessment: it is defined by a P_{aO_2} <60 mmHg (<7.98 kPa) and/or P_{aCO_2} >45 mmHg (>5.99 kPa). These values are not rigid; they must serve as a general guide in combination with the patient's history and clinical evaluation.

Respiratory failure may be acute, chronic or acute on chronic, with the clinical presentation being quite different between these types.

- Acute respiratory failure (ARF) may be life-threatening in clinical presentation, arterial blood gases and acid–base status;
- Chronic respiratory failure is clinically indolent to unapparent, due to mechanisms of compensation for respiratory acidosis.

Respiratory failure due to lung diseases (*e.g.* pneumonia, acute lung injury, acute respiratory distress syndrome (ARDS), emphysema or interstitial lung disease (ILD)) leads to hypoxaemia with normocapnia or even hypocapnia (Type 1 respiratory failure).

Key Points

- Respiratory failure is failure of one or both of the respiratory system's gas exchange or pump functions.
- It is diagnosed by arterial blood gas assessment.
- The clinical presentations of acute, chronic and acute-on-chronic respiratory failure can differ greatly.
- In addition to medical therapy of the underlying condition and oxygen supplementation, mechanical ventilation, either invasive or noninvasive, is the cornerstone of the management in both acute and chronic respiratory failure.

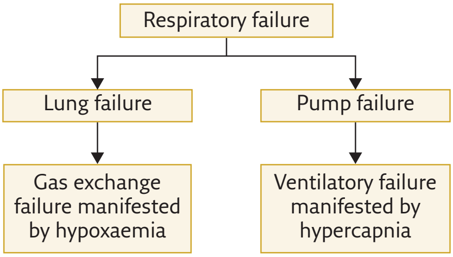

Respiratory failure
Lung failure
Pump failure
Gas exchange failure manifested by hypoxaemia
Ventilatory failure manifested by hypercapnia

Figure 1. Types of respiratory failure. The respiratory system can be considered as consisting of two parts: the lung and the pump. Reproduced and modified from Roussos et al. *(2003).*

Four pathophysiological mechanisms are responsible for hypoxaemic respiratory failure:

- Ventilation/perfusion (V'/Q') ratio inequalities;
- Shunt;
- Diffusion impairment; and
- Hypoventilation.

Hypoxaemia with hypoventilation is characterised by a normal alveolar–arterial oxygen difference, whereas disorders due to any of the other three mechanisms are characterised by a widening of the alveolar–arterial gradient.

Abnormal desaturation of systemic venous blood in the face of extensive lung disease is an important mechanism of hypoxaemia.

Several non-COPD diseases may lead to hypoxaemic ARF, which is defined as a P_{aO_2}/inspiratory oxygen fraction (F_{IO_2}) ratio ≤300 (table 1).

Hypoxaemia is treated with an increase in F_{IO_2} (the lower the V'/Q', the less the effect) and by recruiting airspaces with assisted ventilation. Airspace de-recruitment occurs when the transpulmonary pressure falls below the airspace collapsing or closing pressure, and when the transpulmonary pressure applied during inspiration fails to exceed the airspace opening pressure. Accordingly, airspace opening can be facilitated by increasing the transpulmonary pressure applied at the end of expiration (CPAP or positive end-expiratory pressure (PEEP)) and at the end of inspiration (inspiratory positive airway pressure).

Failure of the pump (*e.g.* neuromuscular diseases or opiate overdose) results in alveolar hypoventilation and hypercapnia with parallel hypoxaemia (Type 2 respiratory failure).

In some diseases (*e.g.* COPD and cardiogenic pulmonary oedema), both conditions may coexist, hypoxaemia usually appearing first.

Table 1. The most common causes of hypoxaemic ARF

Cardiogenic pulmonary oedema
ARDS
Alveolar haemorrhage
Lobar pneumonia
Atelectasis
Pulmonary embolism

Hypercapnic respiratory failure may be the result of CNS depression, functional or mechanical defects of the chest wall, an imbalance of energy demands and supplies of the respiratory muscles, and/or adaptation of central controllers in order to prevent respiratory muscle injury and avoid or postpone fatigue (table 2). Hypercapnic respiratory failure may occur either acutely, insidiously or acutely upon a chronic carbon dioxide retention. In all these conditions, the pathophysiological common mechanism is reduced alveolar ventilation for a given value of carbon dioxide production.

Acute exacerbations of COPD (AECOPD) are periods of acute worsening that greatly affect the health status of patients, with an increase in hospital admissions and mortality. Estimates of in-patient mortality range from 4% to 30% but patients admitted due to ARF experience a higher rate, in particular elderly patients with comorbidities (up to 50%) and those requiring intensive care unit admission (11–26%).

Many causes may potentially be involved in determining ARF during an AECOPD, such as bronchial infections, bronchospasm, left ventricular failure, pneumonia, pneumothorax and thromboembolism. Acute-on-chronic respiratory failure due to

Table 2. Causes of acute hypercapnia

- **Decreased central drive**
  - Drugs
  - CNS diseases
- **Altered neural and neuromuscular transmission**
  - Spinal cord trauma
  - Myelitis
  - Tetanus
  - Amyotrophic lateral sclerosis (ALS)
  - Poliomyelitis
  - Guillain–Barré syndrome
  - Myasthenia gravis
  - Organophosphate poisoning
  - Botulism
- **Muscle abnormalities**
  - Muscular dystrophies
  - Disuse atrophy
  - Prematurity
- **Chest wall and pleural abnormalities**
  - Acute hyperinflation
  - Chest wall trauma
- **Lung and airway diseases**
  - Acute asthma
  - AECOPD
  - Cardiogenic and noncardiogenic oedema
  - Pneumonia
  - Upper airway obstruction
  - Bronchiectasis
- **Other causes**
  - Sepsis
  - Circulatory shock

AECOPD is characterised by the worsening of hypoxaemia, and a variable degree of hypercapnia and respiratory acidosis. The capacity of the patient to maintain acceptable gas exchange during an AECOPD or the development of ARF depends both on the severity of the precipitating cause and on the degree of physiological dysfunction during the stable state, and the subsequent physiological reserve. Worsening of V'/Q' mismatching is probably the leading mechanism in the occurrence of the hypoxaemia by the enlargement of physiological dead space and the rise of wasted ventilation. The increase in airway resistance and the need for a higher V'_E may result in expiratory flow limitation, dynamic hyperinflation and related intrinsic PEEP with subsequent increased inspiratory threshold load and dysfunction of the respiratory muscles, which may lead to their fatigue. A rapid shallow breathing pattern may ensue in attempting to maintain adequate alveolar volume (V_A) when these additional resistive, elastic and inspiratory threshold loads are imposed on weakened respiratory muscles. Nevertheless, despite increased stimulation of the respiratory centres and large negative intrathoracic pressure swings, carbon dioxide retention and acidaemia may occur. Dyspnoea, right ventricular failure and encephalopathy characterise severe AECOPD complicated by ARF. Arterial pH reflects the acute worsening of V_A and, regardless of the chronic P_{aCO_2} level, it represents the best marker of the ARF severity. Figure 2 shows a schematic representation of the sequence of responsible mechanisms that lead to acute-on-chronic respiratory failure in COPD patients.

Besides medical treatment of the underlying disease, oxygen supplementation and, eventually, ventilator assistance are appropriate therapy for acute-on-chronic respiratory failure. The goal of assisted ventilation (either invasive or noninvasive) during AECOPD is to unload the respiratory muscles and to reduce carbon dioxide by increasing V_A, thereby stabilising arterial pH until the underlying problem can be reversed. More recently extracorporeal membrane oxygenation, extracorporeal carbon dioxide removal and high nasal flow therapy have been introduced in the management of respiratory failure.

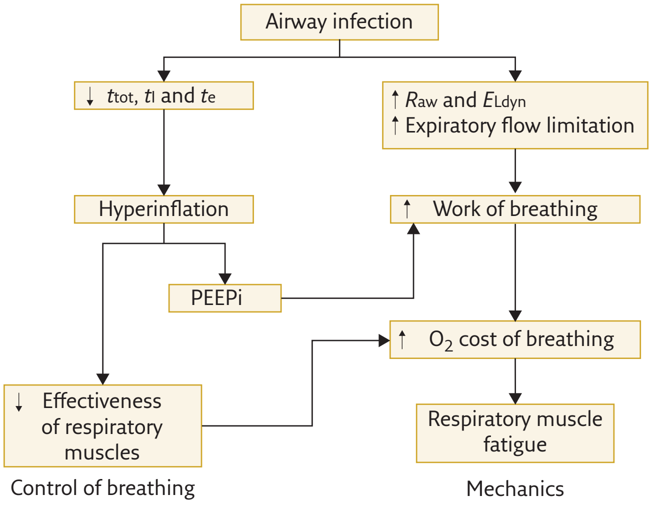

Airway infection
↓ t_{tot}, t_I and t_E
↑ R_{aw} and E_{Ldyn}
↑ Expiratory flow limitation
Hyperinflation
↑ Work of breathing
PEEPi
↑ O_2 cost of breathing
↓ Effectiveness of respiratory muscles
Respiratory muscle fatigue
Control of breathing
Mechanics

Figure 2. Schematic representation of the sequence of responsible mechanisms that lead to acute-on-chronic respiratory failure in COPD patients. t_{tot}*: total respiratory cycle time;* t_I*: inspiratory time;* t_E*: expiratory time;* R_{aw}*: airway resistance;* E_{Ldyn}*: dynamic elastance of the lung; PEEPi: intrinsic PEEP; ↓: decrease; ↑: increase. Reproduced and modified from Roussos* et al. *(2003).*

Further reading

- Bellani G, *et al.* (2016). Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*; 315: 788–800.
- Del Sorbo L, *et al.* (2015). Extracorporeal CO2 removal in hypercapnic patients at risk of noninvasive ventilation failure: a matched cohort study with historical control. *Crit Care Med*; 43: 120–127.
- Dixit D, *et al.* (2015). Acute exacerbations of chronic obstructive pulmonary disease: diagnosis, management, and prevention in critically ill patients *Pharmacotherapy*; 35: 631–648.
- Fan E, *et al.* (2018). Acute respiratory distress syndrome: advances in diagnosis and treatment. *JAMA*; 319: 698–710.
- Fraser JF, *et al.* (2016). Nasal high flow oxygen therapy in patients with COPD reduces respiratory rate and tissue carbon dioxide while increasing tidal and end-expiratory lung volumes: a randomised crossover trial. *Thorax*; 71: 759–761.
- Gayan-Ramirez G, *et al.* (2013). Mechanisms of striated muscle dysfunction during acute exacerbations of COPD. *J Appl Physiol (1985)*;114: 1291–1299.
- Henderson WR, *et al.* (2017). Fifty years of research in ARDS. Respiratory mechanics in acute respiratory distress syndrome. *Am J Respir Crit Care Med*; 196: 822–833.
- Koutsoukou A, *et al.* (2006). Acute and chronic respiratory failure: pathophysiology and mechanics. *In:* Fein AM, *et al.*, eds. Respiratory Emergencies. London, Hodder Arnold; pp. 17–30.
- Laghi F, *et al.* (2012). Auto-PEEP in respiratory failure. *Minerva Anestesiol*; 78: 201–221.
- Pisani L, *et al.* (2017). Change in pulmonary mechanics and the effect on breathing pattern of high flow oxygen therapy in stable hypercapnic COPD. *Thorax*; 72: 373–375.
- Pham T, *et al.* (2017). Mechanical ventilation: state of the art. *Mayo Clin Proc*; 92: 1382–1400.
- Roussos C, *et al.* (2003). Respiratory failure. *Eur Respir J*; 22: Suppl. 47, 3s–14s.
- Trudzinski FC, *et al.* (2016). Outcome of patients with interstitial lung disease treated with extracorporeal membrane oxygenation for acute respiratory failure. *Am J Respir Crit Care Med*; 193: 527–533.

NIV in acute respiratory failure

Anita K. Simonds

NIV is a key management tool in patients with acute hypercapnic respiratory failure, and meta-analyses confirm it markedly reduces mortality and morbidity in acidotic hypercapnic exacerbations of COPD. NIV may also be used in other causes of acute ventilatory failure, such as neuromuscular disease and bronchiectasis, but these indications have not been subject to large randomised controlled trials (RCTs). A more limited role in hypoxaemic respiratory failure is described here. Levels of evidence to support NIV use in acute respiratory failure are shown in table 1.

These levels of evidence align with the ERS/American Thoracic Society (ATS) acute NIV guidelines (2017), which provide a strong recommendation for acute NIV in acute hypercapnic exacerbations of COPD and acute cardiogenic pulmonary oedema. Conditional recommendation for NIV is given in immunocompromised patients in acute respiratory failure, for post-operative high-risk patients to prevent reintubation, for palliative care purposes and to wean hypercapnic patients from invasive ventilation. In contradistinction, a conditional recommendation not to use NIV was made in the situation to prevent hypercapnia in a COPD exacerbation (as there is no evidence of benefit) and in post-extubation respiratory failure where NIV use may delay reintubation.

Key points

- NIV is the gold standard therapy in acute dyspnoeic COPD patents with a pH <7.35 and P_{aCO_2} >45 mmHg (6.0 kPa), and has been shown to halve mortality in this situation. Some guidelines suggest P_{aCO_2} should be >49 mmHg (6.5 kPa).
- Patients with an acute exacerbation of COPD and pH <7.30 being treated with NIV should be managed in a high-dependency or intensive care unit as they are at risk of deterioration and requirement for invasive ventilation.
- In acute hypoxaemic respiratory failure, NIV and entrained oxygen therapy may be tried initially but if improvement in arterial blood gas tensions and dyspnoea do not occur rapidly, urgent consideration should be given to progression to invasive ventilation.
- High-flow nasal cannula oxygen is an option in patients with acute hypoxaemic respiratory failure.
- A combination of NIV and cough assistance with insufflation–exsufflation may be helpful in neuromuscular patients with acute chest infection and reduced cough efficacy.

Table 1. Levels of evidence for use of NIV in acute respiratory failure

Strong evidence (level A)
Acute exacerbations of COPD
To facilitate weaning of COPD
Acute cardiogenic pulmonary oedema (*c.f.* CPAP)
Immunocompromised patients
Reasonable evidence (level B)
Post-operative respiratory failure
'Do not intubate' patients
Upper airway obstruction, OSA, obesity, hypoventilation
CF
Case series/reports
Restrictive disorders
Acute respiratory distress syndrome

See Rochwerg *et al.* (2017) for further details.

NIV in acute exacerbations of COPD

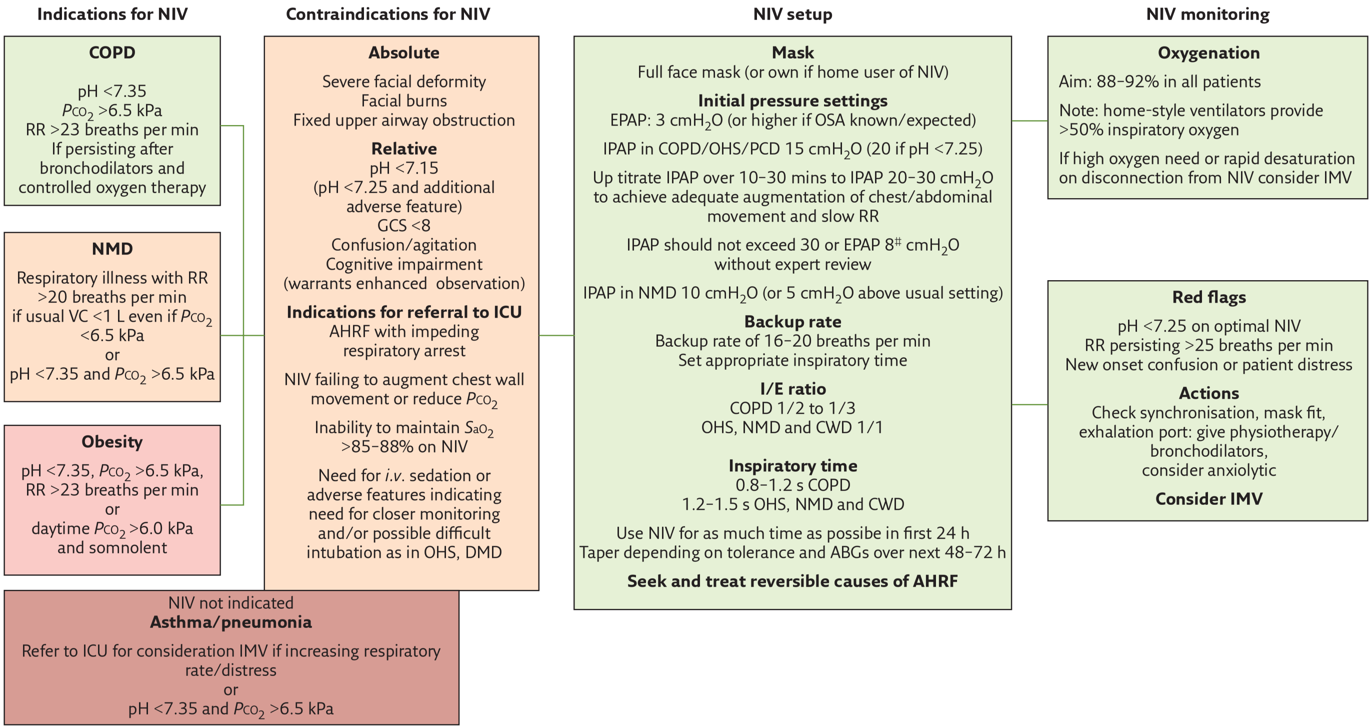
NIV reduces endotracheal intubation rate, and decreases intensive care unit (ICU) and hospital duration of stay in acute acidotic exacerbations of COPD; therefore, it should be available in all respiratory centres that admit COPD patients with exacerbations. In a RCT (Plant *et al.*, 2000) carried out on a general respiratory ward, NIV halved mortality from 20% to 10%, compared with standard COPD care. In patients who are already intubated, prompt extubation onto NIV reduces the duration of ventilation and ICU stay, and increases survival. This is largely due to the fact that endotracheal tube-related nosocomial infections are reduced. Patients are also able to eat and drink normally, and mobilise quicker. Most studies show improvements in arterial blood gases (ABGs) over the first hour of therapy, and falls in carbon dioxide tension and respiratory rate have been shown to predict the success of therapy. Dyspnoea may decrease more rapidly with NIV than with conventional therapy.

Criteria to initiate NIV

NIV should be used in tachypnoeic, dyspnoeic acute COPD patients with a pH <7.35 and P_{aCO_2} >45 mmHg (6.0 kPa). In severe acidotic exacerbations (pH <7.30), the risk of NIV failure and need for intubation are higher but, providing patients are carefully monitored, NIV in a high-dependency unit or ICU may be tried first, as a failed trial of NIV leading to endotracheal intubation does not lead to higher mortality. Relative contraindications to NIV include mental obtundation due to severe hypercapnia, poor cough and bulbar function, upper airway obstruction, multiple comorbidities, and a very high severity score. There is no evidence to support the use of NIV to prevent hypercapnia in COPD exacerbations, as indicated earlier.

Practicalities of ventilator settings

Bilevel positive pressure devices are most commonly used together with full-face masks to obviate leaks from the mouth. Inspiratory positive airway pressure (IPAP) is set to control P_{aCO_2} and reduce the work of breathing; expiratory positive airway pressure (EPAP) is set to overcome episodes of upper airway obstruction and recruit alveoli. A back-up rate a few breaths below the patient's spontaneous breathing rate is usually chosen. Oxygen therapy should be entrained into the circuit as proximally as possible to the mask in order to titrate to the prescribed S_{aO_2} (*e.g.* 88–92%) (figure 1).



Indications for NIV

COPD

pH <7.35
P_{CO_2} >6.5 kPa
RR >23 breaths per min
If persisting after
bronchodilators and
controlled oxygen therapy

NMD

Respiratory illness with RR
>20 breaths per min
if usual VC <1 L even if P_{CO_2}
<6.5 kPa
or
pH <7.35 and P_{CO_2} >6.5 kPa

Obesity

pH <7.35, P_{CO_2} >6.5 kPa,
RR >23 breaths per min
or
daytime P_{CO_2} >6.0 kPa
and somnolent

NIV not indicated
Asthma/pneumonia

Refer to ICU for consideration IMV if increasing respiratory
rate/distress
or
pH <7.35 and P_{CO_2} >6.5 kPa

Contraindications for NIV

Absolute

Severe facial deformity
Facial burns
Fixed upper airway obstruction

Relative

pH <7.15
(pH <7.25 and additional
adverse feature)
GCS <8
Confusion/agitation
Cognitive impairment
(warrants enhanced observation)

Indications for referral to ICU

AHRF with impeding
respiratory arrest

NIV failing to augment chest wall
movement or reduce P_{CO_2}

Inability to maintain S_{aO_2}
>85–88% on NIV

Need for *i.v.* sedation or
adverse features indicating
need for closer monitoring
and/or possible difficult
intubation as in OHS, DMD

NIV setup

Mask

Full face mask (or own if home user of NIV)

Initial pressure settings

EPAP: 3 cmH_2O (or higher if OSA known/expected)

IPAP in COPD/OHS/PCD 15 cmH_2O (20 if pH <7.25)

Up titrate IPAP over 10–30 mins to IPAP 20–30 cmH_2O
to achieve adequate augmentation of chest/abdominal
movement and slow RR

IPAP should not exceed 30 or EPAP 8$^{\#}$ cmH_2O
without expert review

IPAP in NMD 10 cmH_2O (or 5 cmH_2O above usual setting)

Backup rate

Backup rate of 16–20 breaths per min
Set appropriate inspiratory time

I/E ratio

COPD 1/2 to 1/3
OHS, NMD and CWD 1/1

Inspiratory time

0.8–1.2 s COPD
1.2–1.5 s OHS, NMD and CWD

Use NIV for as much time as possibe in first 24 h
Taper depending on tolerance and ABGs over next 48–72 h

Seek and treat reversible causes of AHRF

NIV monitoring

Oxygenation

Aim: 88–92% in all patients

Note: home-style ventilators provide
>50% inspiratory oxygen

If high oxygen need or rapid desaturation
on disconnection from NIV consider IMV

Red flags

pH <7.25 on optimal NIV
RR persisting >25 breaths per min
New onset confusion or patient distress

Actions

Check synchronisation, mask fit,
exhalation port: give physiotherapy/
bronchodilators,
consider anxiolytic

Consider IMV

Figure 1. Summary of provision of acute NIV. P_{CO_2}: carbon dioxide tension; RR: respiratory rate; NMD: neuromuscular disease; VC: vital capacity; IMV: invasive mechanical ventilation; GCS: Glasgow coma scale; DMD: Duchenne muscular dystrophy; PCD: primary ciliary dyskinesia; I/E: inspiratory/expiratory; CWD: chest wall disease. $^{\#}$: possible need for EPAP >8 cmH_2O in severe OHS (BMI >35 $kg{\cdot}m^{-2}$), lung recruitment (e.g. hypoxia in severe kyphoscoliosis), opposite intrinsic positive end-expiratory pressure in severe airflow obstruction or to maintain adequate pressure support when high EPAP required. Reproduced and modified from Davidson et al. *(2016) with permission from the publisher.*

'Intelligent' ventilators that add either an assured tidal volume or V'_E may be helpful in some patients but have not yet been shown to be superior to expert ventilator setup. Careful attention to mask fit is important as this helps encourage adherence to therapy. Before initiating NIV, advance care planning should take place to clarify whether progression to endotracheal intubation is indicated, and in accordance with the patient's wishes and best interests, in the event of NIV failure. An ERS Task Force survey (Nava *et al.*, 2007) showed that NIV was the ceiling of care in 31% of patients with acute exacerbations of COPD admitted to high-dependency units. As pointed out by Demoule *et al.* (2006), survival in patients with NIV as a ceiling of care is 50–60% for the episode but, 1 year after, mortality is 30%, which is significantly lower than those with no ceiling of care.

NIV in other causes of hypercapnic respiratory failure

NIV is used in acute hypercapnic exacerbations of CF and bronchiectasis. It may be helpful when combined with intensive physiotherapy and other airway clearance techniques (and, indeed, may allow physiotherapy sessions to be extended when these are carried out in patients simultaneously using NIV). NIV can be used to bridge CF patients to transplantation.

NIV may also be used to reduce the work of breathing and improve ABG tensions in patients with respiratory muscle weakness due to neuromuscular conditions such as Duchenne muscular dystrophy, spinal muscular atrophy, myopathies and motor neurone disease. In these situations, if cough peak flow is $<160\ \mathrm{L{\cdot}min^{-1}}$, augmentation of secretion clearance with mechanical insufflation–exsufflation is likely to reduce the risk of intubation.

There are no large RCTs of NIV in acute ventilatory failure in patients with obesity hypoventilation syndrome (OHS). However, comparisons suggest that NIV is more effective than CPAP in patients with significant hypercapnia and superior to endotracheal intubation in those without major comorbidity. EPAP should be titrated to control the OSA/hypopnoea component and IPAP to control $P_{\mathrm{aCO_2}}$. On recovery from an acute hyperacapnic exacerbation, it may be feasible to step down OHS patients from NIV to CPAP, and this should be explored.

NIV in acute hypoxaemic respiratory failure

Acute hypoxaemic respiratory failure (AHRF) occurs in a multiplicity of disorders including pneumonia, acute cardiogenic pulmonary oedema, acute lung injury, acute respiratory distress syndrome, and following immunosuppression, trauma and noxious gas inhalation. As the underlying pathophysiological mechanisms of ventilation–perfusion mismatch, shunt and diffusion difficulties differ from hypoventilation in acute ventilatory failure, one can predict that success rates with NIV will be lower. While ventilatory support is used to reduce the work of breathing, improve $P_{\mathrm{aCO_2}}$ control and recruit alveoli, it also buys time for other definitive therapies to take effect. Buying time may be more swiftly effective in, for example, acute pulmonary oedema, where diuretic and vasodilator therapy may be added, or pneumonia, where antibiotics can be introduced, compared with acute lung injury, where there is no specific therapy.

In several RCTs of patients with AHRF of mixed aetiology, NIV reduced the need for intubation, ICU stay and mortality. However, results are less clear-cut in pneumonia, where one study (Confalonieri *et al.*, 1999) showed a subgroup of patients with COPD and community-acquired pneumonia (CAP) experienced less intubation than the pneumonia group as a whole, and a further study (Jolliet *et al.*, 2001) suggests that those with severe CAP experienced a higher intubation rate and longer ICU stay. In highly infectious causes of pneumonia (*e.g.* severe acute respiratory syndrome (SARS) and pandemic influenza), special measures are required when using NIV. Although NIV is categorised as an aerosol-generating procedure by some authorities, further work (Simonds *et al.*, 2010) suggests it mainly generates large droplets (>10 µm in diameter). However, special precautions should be taken, including using personal protective equipment (PPE), a high-efficiency N95 microbial filter between the mask and exhalation valve, low pressures, and close attention to mask fit. The ERS/ATS NIV guidelines make no recommendation either way for or against NIV use in acute pandemics and it should be recognised that AHRF may progress rapidly in these patients, mandating the need for intubation and invasive ventilation.

In acute cardiogenic pulmonary oedema, there have been several meta-analyses (Winck *et al.*, 2006; Masip *et al.*, 2005; Peter *et al.*, 2006) and a large RCT (Crane *et al.*, 2004). Results suggest that use of NIV and CPAP can reduce breathlessness and improve ABG tensions, and in the meta-analyses, NIV did reduce intubation; however, in the large RCT, which contained more patients than were included in the meta-analyses, there was no difference in mortality at 7 days between oxygen therapy, NIV and CPAP, and no differences in outcomes when NIV and CPAP were compared. A consensus is that medical therapy with nitrates is crucial first-line treatment, with the addition of CPAP in those with marked respiratory distress and NIV for those who are hypercapnic due to high work of breathing and/or concomitant COPD or neuromuscular disorder.

In all the causes of AHRF discussed here, NIV with entrained oxygen therapy may be tried initially but close monitoring is required and, if ABG tensions and dyspnoea are not relieved within the first hour of therapy or the patient's condition rapidly deteriorates, progression to use of invasive ventilation should be urgently considered.

Stopping NIV

NIV can be withdrawn 1) following a successful period of therapy when the patient no longer needs it or 2) if the intervention fails and an alternative management strategy is required.

- In acute hypercapnic exacerbations of COPD, early success of NIV is evidenced by correction of pH, a fall in respiratory rate and relief of dyspnoea. P_{aCO_2} should gradually fall and P_{aO_2} improve towards baseline levels when well. Recovery time is inevitably variable but increasing periods off NIV during the day while ensuing P_{aCO_2} does not climb is a pragmatic way forward. Continuing NIV at night for a short period further (in view of nocturnal hypoventilation, which will worsen diurnal ABG tensions during sleep) may also help restore sleep quality and aid recovery. Some centres carry out overnight monitoring of S_{aO_2} and transcutaneous carbon dioxide tension off NIV to ensure no significant residual hypoventilation remains before finally withdrawing NIV. As indicated in the chapter on long-term ventilation, hyperacapnia persisting ≥2 weeks after an acute exacerbation of COPD is an indication for long-term NIV. Domiciliary NIV should also be considered in neuromuscular patients and those with OHS who remain persistently hypercapnic on withdrawal of NIV.
- NIV failure rates will depend on a number of factors including the underlying cause of respiratory failure, its severity, and related issues such as inability of the patient to tolerate the interface/ventilation, poor secretion clearance, hypoxaemic respiratory failure and comorbidities. Primary NIV failure is ascribed to failure of

NIV to work from a practical point of view (*e.g.* due to poor tolerance or settings inadequate). Secondary NIV failure occurs when despite an initial response, the patient continues to deteriorate due to progression of disease. Here, the outcome is less good. It is important to recognise NIV failure by close monitoring. Primary failure may be correctable by adjusting ventilator settings, or changing the interface or ventilator mode. Management of secondary failure will depend on the patient's wishes, prognosis and advance care plan. Intubation and invasive ventilation may be required but if NIV is the ceiling of care, a switch to palliative care with the focus on symptom relief is important. Controlled oxygen therapy, opiates and possibly high-flow nasal cannula (HFNC) oxygen delivery may all have a role.

NIV *versus* HFNC oxygen delivery

HFNC systems provide a high-flow (40–60 L·min^{-1}) humidified oxygen/air mix delivered by nasal cannula. Trials comparing HFNC and NIV therapy in acute hypoxaemic patients in the ICU suggest better survival rates and more ventilator-free days in the HFNC group compared to NIV. In post-extubation patients, HFNC seems better tolerated and noninferior to NIV, although difficulty in blinding and poor NIV adaptation may be confounding factors (Helviz *et al.*, 2018). HFNC therapy is certainly a noninvasive option in AHRF patients and research in this area is ongoing.

HFNC therapy has also been used on an empirical basis in case series of patients with hypercapnic respiratory failure who are unable to tolerate NIV. There are no trials yet in this area and careful monitoring is required to ensure hypercapnia is controlled.

Implementation of guidelines and providing an acute NIV service

Despite recent guidelines, a current report (Acute Non-Invasive Ventilation: Inspiring Change; NCEPOD, 2017) shows deficiencies in the provision of NIV. Key areas for improvement are poor documentation, lack of pressure titration, delay in initiating NIV, poor titration of oxygen therapy, inadequate monitoring and lack of senior consultant review. In a UK study, 38% of those prescribing NIV or changing settings did not have documented competency training. These are important areas for centres to address to improve standards of care. Regular audits and checklists should also be used to optimise outcomes from acute NIV.

Further study

The ERS NIV simulator provides skills training in initiating managing acute and chronic NIV. It can be accessed at ERS e-learning resources: www.ers-education.org/e-learning/simulators.aspx

Further reading

- Confalonieri M, *et al.* (1999). Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. *Am J Respir Crit Care Med*; 160: 1585–1591.
- Crane SD, *et al.* (2004). Randomised controlled comparison of continuous positive airways pressure, bilevel non-invasive ventilation, and standard treatment in emergency department patients with acute cardiogenic oedema. *Emerg Med J*; 21: 155–161.
- Davidson AC, *et al.* (2016). BTS/ICS guidelines for ventilatory management of acute hypercapnic respiratory failure in adults. *Thorax*; 71: Suppl., 2: ii1–ii35.
- Demoule A, *et al.* (2006). Increased use of noninvasive ventilation in French intensive care units. *Int Care Med*; 32: 1747–1755.

- Helviz Y, *et al.* (2018). A systematic review of high flow nasal cannula for adult patients. *Critical Care*; 22: 71.
- Jolliet P, *et al.* (2001). Non-invasive pressure support ventilation in severe community-acquired pneumonia. *Int Care Med*; 27: 812–821.
- Masip J, *et al.* (2005). Noninvasive ventilation in acute cardiogenic pulmonary edema: systematic review and meta-analysis. *JAMA*; 294: 3124–3130.
- Moretti M, *et al.* (2000). Incidence and causes of non-invasive mechanical ventilation failure after initial success. *Thorax*; 55: 819–825.
- Nava S, *et al.* (2007). End of life decision-making in respiratory intermediate care units: a European survey. *Eur Respir J*; 30: 156–164.
- NCEPOD (2017). Acute Non-Invasive Ventilation: Inspiring Change. London, National Confidential Enquiry into Patient Outcome and Death; available from http://www.ncepod.org.uk/2017report2/downloads/InspiringChange_FullReport.pdf.
- Peter JV, *et al.* (2006). Effect of non-invasive positive pressure ventilation (NIPPV) on mortality on patients with acute cardiogenic pulmonary oedema: a meta-analysis. *Lancet*; 367: 1155–1163.
- Plant PK, *et al.* (2000). Early use of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet*; 355: 1931–1935.
- Rochwerg B, *et al.* (2017). Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J*; 50: 1602426.
- Simonds AK, *et al.* (2010). Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: Implications for the management of pandemic influenza and other airborne infections. *Health Tech Assess*; 14: 131–172.
- Winck JC, *et al.* (2006). Efficacy and safety of non-invasive ventilation in the treatment of acute cardiogenic pulmonary oedema – a systematic review and meta-analysis. *Crit Care*; 10: R69.

Idiopathic pulmonary fibrosis

Pier-Valerio Mari, Athol Wells and Luca Richeldi

The interstitial lung diseases (ILDs) are a heterogeneous group of disorders with remarkably different prognoses and clinical histories. Most ILDs are characterised by interstitial inflammation and/or fibrosis. Idiopathic pulmonary fibrosis (IPF), currently viewed as a purely fibrotic disorder, is the most prevalent ILD (comprising 20–50% of all ILDs) and has the worst outcome with a 5-year survival that is lower than most malignant diseases. IPF is a chronic, progressive, fibrosing pneumonia of unknown cause that leads to severe dyspnoea, impairment of lung function and death from respiratory failure. In recent years there have been major changes in the diagnosis and management of IPF.

Epidemiology

The epidemiology of IPF has been broadly studied using large databases of primary care data allowing researchers to assess the incidence, prevalence and survival of IPF. IPF is the most common of all the ILDs and the incidence appears to be higher in Europe and North America (from 3 to 9 cases per 100 000 person-years) when compared with South America or East Asia (4 cases per 100 000 person-years). Population-based estimates of IPF burden in the UK demonstrated a near 80% increase of incidence from 2000 to 2012, with the increase not explained by better IPF recognition by clinicians and not dependent upon age or sex. Environmental challenges may play a

Key points

- Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrotic interstitial lung disease (ILD).
- IPF is the most common of all the ILDs.
- The clinical presentation of IPF includes: dyspnoea on exertion, dry cough and Velcro-like crackles.
- IPF is a diagnosis that requires the exclusion of other known causes of ILDs.
- Usual interstitial pneumonia (UIP) is the typical pattern of a HRCT scan or histopathological sample.
- Current IPF guideline provide a strong recommendation against the use of corticosteroids, immunosuppressants and *N*-acetylcysteine.
- Nintedanib and pirfenidone are the antifibrotics currently used in pharmacological management of IPF.

central role in IPF: epidemiological studies show that environmental exposure to coal dust, wood dust and pollution are all associated with an increased incidence of IPF.

Pathophysiology and risk factors

Risk factors for IPF include past exposures resulting in epithelial injury and genetic factors. A single-nucleotide polymorphism (rs35705950) associated with IPF in approximately half of cases is located in the promoter region of *MUC5B*, coding for a glycoprotein required for airway clearance. Short telomere length is also associated with IPF and there is ongoing research into genes involved in the maintenance of telomere length (*e.g. TERC*) and cell adhesion (*e.g. AKAP13*). It is believed that familial IPF is responsible for at least 10% of IPF cases. Other risk factors include male sex, cigarette smoking and older age.

The onset of IPF is believed to be triggered by various forms of epithelial damage, which may include infective insults and microaspiration from gastro-oesophageal regurgitation. Air pollution and occupational exposures may also play a key role.

The pathogenesis of disease progression in IPF is not fully understood. Current conceptual thinking emphasises the role of subclinical and recurrent epithelial injury imposed on accelerating epithelial ageing leading to aberrant repair of the alveolus and collagen deposition in the interstitium by myofibroblasts. The senescence of alveolar cells and fibroblasts may be pivotal in promoting lung fibrosis. Oxidative stress injury or alterations in telomere maintenance lead to production of profibrotic mediators.

Clinical features

IPF should be suspected in adults presenting with chronic exertional dyspnoea, dry cough, or Velcro-like crackles on medical evaluation. Typically, dyspnoea on exertion is insidiously progressive over months or years. Not infrequently, IPF is initially misdiagnosed as chronic heart failure or COPD. A spirometric restrictive ventilatory defect is classically present in moderately severe IPF. However, in mild IPF, FVC values are commonly in the normal range, although associated with an isolated reduction in T_{LCO}. Based on correlations with CT disease extent and the prediction of mortality, disease severity is better captured by T_{LCO} values than by other pulmonary function tests. A reduction in T_{LCO} that is disproportionate to lung volumes (quantified using the K_{CO} or FVC/T_{LCO} ratio) is suggestive of concurrent emphysema or pulmonary vasculopathy. Chest radiographic appearances may be normal or show nonspecific findings in the early stages, such as reticular shadowing of the lung peripheries or hazy opacities, along with a reduction of inspiratory lung volumes in the advanced stage.

Diagnosis

The diagnosis of IPF may be challenging. In 2018, the official clinical practice guidelines were released by an international task force involving the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society and Latin American Thoracic Society. The guidelines state that the diagnosis of IPF requires:

1) Exclusion of other known causes of ILD (*i.e.* exposures, medications, connective tissue disease (CTD))

and one of either criteria 2 or 3:

2) Presence of a usual interstitial pneumonia (UIP) pattern on chest HRCT
3) Specific combinations of HRCT patterns and histopathology patterns in patients subjected to lung tissue sampling

In patients with progressive dyspnoea and a restrictive ventilatory defect or findings compatible with ILD on physical examination, a HRCT scan should be performed. The presence of a radiological UIP pattern is typically required to establish the diagnosis of IPF. The features of a 'definite UIP pattern', synonymous with a UIP histological pattern, consist of bilateral, predominantly basal and sub-pleural, reticulation and honeycombing. A 'probable UIP pattern' is defined as bilateral, predominantly basal and sub-pleural reticulation, associated with traction bronchiectasis but without honeycombing. In the correct clinical context (age >65 years, no overt trigger of fibrosis), a probable UIP pattern is strongly suggestive of an underlying histological UIP pattern. Upper-mid lung predominance, subpleural sparing, cysts, mosaic attenuation, consolidation or extensive ground glass are atypical for IPF and denote an "indeterminate" UIP pattern.

Thus, IPF may be diagnosed with confidence in the absence of a known cause for a fibrotic process when there is definite UIP on CT or, in patients aged over 65 years, probable UIP on CT. In other circumstances, clinical data and imaging are generally insufficient for a confident diagnosis. Bronchoalveolar lavage (BAL) is useful (in excluding hypersensitivity pneumonitis by virtue of the absence of a BAL lymphocytosis) when a confident diagnosis of IPF is not reached. A histological UIP pattern at surgical biopsy (or transbronchial lung cryobiopsy in some cases) usually allows a confident IPF diagnosis. To improve diagnostic confidence, a multidisciplinary team discussion may be valuable and typically involves pulmonologists, radiologists, pathologists and, sometimes, rheumatologists when an occult underlying CTD is suspected.

Treatment

The management of IPF has evolved considerably during the past decade. Nonpharmacological treatment includes smoking cessation, age-appropriate vaccination, supplemental oxygen in case of hypoxaemia at rest or on exertion, physiotherapy, nutrition management, treatment of comorbidities and evaluation for lung transplantation in those with end-stage conditions. Notable recent advances have been made in the pharmacological treatment of IPF (table 1).

Table 1. Pharmacological management of IPF

	Nintedanib	**Pirfenidone**
Target	Inhibition of tyrosine kinase	Inhibition of transforming growth factor (TGF)-β and collagen production
Dosage	150 mg, oral, two times per day	801 mg, oral, three times per day
Side-effects (common)	Diarrhoea	Nausea, photosensitivity
Cautions	Bleeding risk: anticoagulants should be avoided	Inhibitors of CYP-1A2: can raise drug levels (fluoroquinolones) Inducers of CYP-1A2: can lower drug levels (cigarette smoking and omeprazole)
Monitoring and follow-up	Need for liver-function monitoring	

A strong recommendation has been given by guidelines against the use of prednisone in combination with azathioprine and *N*-acetylcysteine due to a major increase in overall mortality and respiratory hospitalisation in a controlled trial. To date, two medications (pirfenidone and nintedanib) have been approved and show safety and efficacy in placebo-controlled, randomised controlled trials (RCTs). Both slow the rate of FVC decline by ~50% over 52 weeks: nintedanib also appears to reduce the rate of acute exacerbations. No reduction of mortality has been proved in a RCT, but pooled analysis suggests a reduction of overall mortality in IPF. Nintedanib is a tyrosine kinase inhibitor that targets multiple growth factor pathways (vascular endothelial growth factor, fibroblast growth factor and platelet-derived growth factor). Side-effects include diarrhoea, which can be controlled with antidiarrhoeal agents. Pirfenidone has various anti-inflammatory and antifibrotic effects such as the downregulation of profibrotic factors and reduction of fibroblast proliferation. Common side-effects are anorexia, nausea and vomiting, and a photosensitive rash. Liver function must be tested at baseline and monitored regularly with both drugs. Recommendation of one agent over the other cannot be given and no head-to-head data are available. The efficacy of combination treatment has yet to be validated.

Acute exacerbation of IPF

Patients with IPF may experience an acute exacerbation, an acceleration of the disease over days to weeks, that leads to a significant decline in lung function, with lung injury (diffuse alveolar damage) superimposed on fibrotic lung. The following features have been recently proposed as criteria:

- previous or concurrent diagnosis of IPF,
- unexplained worsening of dyspnoea within the past 30 days,
- new bilateral ground-glass opacity or consolidation on the chest HRCT scan.

An acute exacerbation can be diagnosed even when there is a proven respiratory infection, but exclusion of cardiac failure is also required. Mortality approximates 60% at 1 month and up to 80% at 3 months. No current treatment has proven efficacy: nonetheless high-dose corticosteroids associated with broad-spectrum antibiotics are widely used and recommended by current guidelines, despite the lack of robust evidence.

Further reading

- Collard HR, *et al.* (2016). Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. *Am J Respir Crit Care Med*; 194: 265–275.
- King TE Jr., *et al.* (2014). A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med*; 370: 2083–2092.
- Lederer DJ, *et al.* (2018). Idiopathic pulmonary fibrosis. *N Engl J Med*; 378: 1811–1823.
- Lynch DA, *et al.* (2018). Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. *Lancet Respir Med*; 6: 138–153.
- Raghu G, *et al.* (2018). Diagnosis of idiopathic pulmonary fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med*; 198: e44–e68.
- Richeldi L, *et al.* (2014). Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*; 370: 2071–2082.

Hypersensitivity pneumonitis

Torben Sigsgaard and Anna Rask-Andersen

Hypersensitivity pneumonitis (HP), also known as allergic alveolitis, is an immunologically mediated inflammatory lung disease in the lung parenchyma induced by the inhalation of a variety of (predominantly organic) particles and characterised by hypersensitivity to the antigens. The disease is usually named colourfully after the environment in which it occurs (*e.g.* farmer's lung and bird fancier's lung), and has been reported in over 30 different occupations and environments. Regardless of the causative agents or its environmental setting, the pathogenesis and clinical manifestations of the disease are similar. The hallmark of the disease is a massive lymphocytic inflammation with accumulation of activated T-lymphocytes in the lung interstitium.

Epidemiology

In a large, general population-based cohort of HP patients from the UK, the overall incidence rate was ~1 per 100000 population and in Japan, the summer-type HP occurs every year in ~1 per million population. Most other studies have focused on the risk of developing clinical disease amongst subsets of the population with high levels of exposure to antigens. For example, the incidence of farmer's lung in Sweden in the 1980s was 20 per 100000 person-years. However, there has been a decrease in the incidence of farmer's lung due to changes in farming practice (hay making replaced by silage bags). In the UK, metalworking fluid exposure has become the commonest recognised cause of occupational HP, having been rare before 2000. Originally, mineral oils were used to cool and lubricate metal being ground, drilled or otherwise worked on. These have been replaced by water-based emulsions favouring

Key points

- Hypersensitivity pneumonitis (HP) is an immunologically mediated inflammatory lung disease of the parenchyma.
- HP is induced by the inhalation of a variety of organic or inorganic antigens, and is characterised by hypersensitivity to antigens.
- The main characteristic of HP is massive lymphocytic inflammation with accumulation of activated T-lymphocytes in the lung interstitium in the subacute situation. This picture can be less characteristic in chronic HP.
- The only treatment is to avoid exposure to the offending allergen; if the exposure ceases, the symptoms usually subside rapidly but lung function impairment may persist.

microbial growth that is very hard to eradicate. A study from North America showed that common causes of HP were bird or hot-tub exposure.

Risk factors

The first reported HP was farmer's lung, caused by inhalation of microorganisms from infested crops. The disease was first described among farmers in the Nordic countries; however, it has since been described in range of farming operations all over the world, making farming-like operations with decaying organic material one of the exposures to look for when confronted with a case of HP. Another common appearance of HP is bird fancier's lung, caused by exposure to birds (*e.g.* pigeons or parakeets) but exposure to bird antigens might even be from feather bedding and down quilts. Among pigeon breeder's HP, intestinal mucin, a high molecular weight glycoprotein, has been identified as a major antigen.

Host factors

Only a small proportion of individuals exposed to causative agents develop the disease. This has sparked the idea of susceptibility genes. However, so far, no genes have been unequivocally associated with an increased risk of HP.

Smoking seems to protect against HP, although the disease has been described in a small number of smokers. The reason for this protection might be the downregulation of the immune system by tobacco smoke and nicotine. However, smokers that develop HP have a poorer prognosis than non-smokers.

In animal models, virus infection seems to increase the susceptibility of mice towards the antigens and a higher number of virus antigens have been found in the bronchial lavage of HP patients.

Pathological mechanism

Although HP is a well-known disease, the pathogenesis still is only partly understood. When Pepys (1978) found serum precipitating IgG antibodies to mould antigen in many of the cases, it was believed that, for many years, the immune complexes were the basis of the lung changes. However, the presence of precipitins merely reflects the exposure and sensitisation to the specific antigen by the patient, and is not diagnostic of HP.

It is now believed that the disease is driven by a delayed cellular immune response to an inhaled antigen to which the subject had been previously sensitised. The immune mechanism is a Th1 response involving many cell types and a plethora of inflammatory mediators released mostly by activated lymphocytes and alveolar macrophages. A complex formed by soluble antigens and IgG antibodies triggers the complement cascade, and alveolar macrophage activation is induced, resulting in an increase in macrophages. These cells secrete cytokines and chemokines that attract neutrophils in the alveoli and small airways. The number of T-lymphocytes is also increased with a predominance of the $CD8^+$ T-lymphocyte subset resulting in a decrease in the $CD4^+/CD8^+$ ratio (in contrast to observations made in sarcoidosis). Different upregulatory mechanisms result in a stronger interaction between macrophages and T-cells, and more effective antigen presentation.

Symptoms and findings

The predominant symptoms in HP are tiredness, dyspnoea, fever, shivering, an influenza-like feeling, cough, muscle and joint aches, headache, and weight loss.

Radiography of the thorax shows diffuse, fine, nodular shadows, either general or predominantly in the bases. In the early stages, the changes can be difficult to detect but widespread patchy opacities may also be seen on CT/HRCT. Lung function is decreased with a typical restrictive pattern and decreased T_{LCO}, but obstructive patterns might also be seen. Some patients with chronic HP with progressive lung fibrosis develop pulmonary symptom more insidiously over many months and years with or without intermittent aggravation of symptoms such as fever and cough.

Environmental assessment

The origin of the disease is an adverse reaction towards an occupational or environmental factor, so it is imperative to search the patient's environment for this exposure and to minimise further contact with the offending agent (table 1). In many cases it is obvious what the reason might be; for example, a mouldy hay problem occurring after a wet harvest season. In some instances (for some cohorts, >50%), the causal agent might be difficult to find and techniques for the assessment of microorganisms should be employed to assess the exposure to which the patient is exposed.

Diagnosis

The diagnosis of HP relies on an array of nonspecific clinical symptoms and signs developed in an appropriate setting, with demonstration of bilateral patchy infiltrates on chest radiographs and serum precipitating antibodies against offending antigens. Several different diagnostic criteria for HP have been proposed; all have significant problems that limit their utility. After studying a total of 661 HP patients with a stepwise logistic regression, a panel of clinical experts identified the six significant predictors of HP.

Diagnostic criteria of extrinsic allergic alveolitis are as follows:

- Exposure to a known offending antigen
- Symptoms occurring 4–8 h after exposure
- Positive precipitating antibodies to the offending antigen
- Inspiratory crackles on physical examination
- Recurrent episodes of symptoms
- Weight loss

Identifying the causative antigen is crucial for diagnosis, preventive measures and prognosis of HP. A detailed patient history of exposure in their occupational and domestic environments, as well as any regularly visited places, is of utmost importance. The relationship between the exposure and the disease may be obvious in cases of occupational HP but in domestic cases, is often not immediately clear, making identification of the underlying trigger challenging. Identification of serum precipitins may help to clarify exposure. Diagnosing HP with a chronic and insidious course that might not fulfil the criteria above is especially difficult but of importance because of the serious nature of the disease.

Typical HRCT findings are upper and middle lobe-predominant ground-glass opacities, poorly defined centrilobular nodules, mosaic attenuation and air trapping. In chronic HP with fibrosis, the typical findings are upper and middle lobe-predominant fibrosis, peribronchovascular fibrosis, honeycombing, mosaic attenuation, air trapping and centrilobular nodules, with relative sparing of the bases.

Table 1 HP types, with typical causative exposures and antigens

HP type	Exposure	Antigen
Farmer's lung	Mouldy hay	*Saccharopolyspora rectivirgula*
Bagassosis	Mouldy bagasse	*Thermoactinomyces sacchari*
Mushroom worker's lung	Mushroom spores, mushroom compost	Thermophilic actinomycetes
Malt worker's lung	Mouldy barley	*Aspergillus clavatus*, *Faenia rectivirgu*
Humidifier/ air-conditioner lung	Contaminated water reservoirs	Thermophilic actinomycetes
Grain handler's lung	Mouldy grain	*S. rectivirgula*, *Thermoactinomyces vulgaris*
Cheese worker's lung	Cheese mould	*Penicillium casei*
Paprika splitter's lung	Paprika dust	*Mucor stolonifer*
Compost lung	Compost	*Aspergillus* spp.
Peat moss worker's lung	Peat moss	*Monocillium* spp., *Penicilliumcitreonigrum*
Suberosis	Mouldy cork dust	*Penicillium frequentans*
Maple bark stripper's lung	Mouldy wood bark	*Cryptostroma corticale*
Wood pulp worker's lung	Mouldy wood pulp	*Alternaria* spp.
Wood trimmer's disease	Mouldy wood trimmings	*Rhizopus* spp.
Japanese summer-type HP	Indoor air	*Trichosporon cutaneum*
Wind instruments	Humid instruments	Mycobacteria, moulds
Metal grinding	Metalworking fluids	Mycobacteria
Hot tub lung	Mist from hot tubs	Mycobacteria
Bird breeder's lung	Pigeons, parakeets, fowl and rodents	Avian or animal proteins
Mollusc-shell hypersensitivity	Sea snail shells	Shell dust
Chemical worker's lung	Manufacture of plastics, polyurethane foam and rubber	Trimellitic anhydride, diisocyanate, methylene diisocyanate

However, diagnosing HP often poses challenges, even to expert clinicians. Additional investigations (including lung biopsy) are indicated in patients with interstitial diseases in whom the diagnosis remains unclear after initial assessment.

Treatment

The only treatment for allergic diseases is to avoid the exposure to the offending allergen. This can be done in many circumstances, such as when the occurrence is sporadic and not part of the daily work of the patient. However, in some cases (*e.g.* in farmers), it might be difficult to completely avoid the exposure for a range of different reasons. Under such circumstances, respiratory protection can be used to minimise the exposure as much as possible.

The effect of medical treatment on the outcome of HP has been discussed. No evidence-based treatment recommendations are available for HP. Cortisone treatment seems to improve the radiological findings as well as T_{LCO} and should be given to severely ill patients to ameliorate symptoms, but no apparent benefit is derived from long-term treatment. For chronic HP, antifibrotic treatments used for idiopathic pulmonary fibrosis (IPF), immunosuppressants and novel anti-inflammatory/antifibrotic agents have been suggested and are now in clinical trials.

Prognosis

If the exposure ceases, the symptoms usually subside rapidly but lung function impairment may persist for a longer period and become permanent with a restrictive pattern and decreased T_{LCO}. Repeated attacks increase the risk of a poor prognosis. It is therefore important to treat the patient as soon as possible in order to avoid more damage to the lung parenchyma in addition to that already present at the time of diagnosis. Some cases develop into a chronic form with progressive pulmonary fibrosis but that is probably rare.

Differential diagnosis

Infectious lung diseases, both of viral and bacterial origin, as well as other lung diseases such as sarcoidosis, must be ruled out. Another differential diagnosis is organic dust toxic syndrome (ODTS), also known as ‘inhalation fever’: acute, febrile, noninfectious, influenza-like, short-term reactions that can be produced by inhalation of bioaerosols and organic dusts. Symptoms are caused by the release of inflammatory cytokines from the lungs caused by an inhalatory overexposure to aerosols. ODTS is quite a common condition but the prognosis is good and most people have recovered totally without any sequels after 24 h. No treatment is required if the exposure is terminated.

It is especially challenging to distinguish chronic HP with pulmonary fibrosis from IPF, not overlooking occupational and environmental factors that can contribute to the disease. Recent reviews reveal that a sizable proportion of patients initially diagnosed with IPF later received a diagnosis of HP. Furthermore, a population-based study showed a significantly higher incidence of interstitial lung disease (ILD) among pigeon breeders. Hence, there are difficulties in the differential diagnosis between ILD and HP. Drug toxicity is another differential diagnosis that should not be forgotten.

Further reading

- Ando M, *et al.* (1991). Japanese summer-type hypersensitivity pneumonitis. Geographic distribution, home environment, and clinical characteristics of 621 cases. *Am Rev Respir Dis*; 144: 765–769.
- Arya A, *et al.* (2006). Farmer’s lung is now in decline. *Irish Med J*; 99: 203–205.
- Bourke SJ, *et al.* (2001). Hypersensitivity pneumonitis: current concepts. *Eur Respir J*; 18: Suppl. 32, 81s–92s.

- Burge PS (2016). Hypersensitivity pneumonitis due to metalworking fluid aerosols. *Curr Allergy Asthma Rep*; 16: 59.
- Cramer C, *et al.* (2016). Risk of hypersensitivity pneumonitis and interstitial lung diseases among pigeon breeders. *Eur Respir J*; 48: 818–825.
- Hanak V, *et al.* (2007). Causes and presenting features in 85 consecutive patients with hypersensitivity pneumonitis. *Mayo Clinic Proc*; 82: 812–816.
- Lacasse Y, *et al.* (2003). Clinical diagnosis of hypersensitivity pneumonitis. *Am J Respir Crit Care Med*; 168: 952–958.
- Malmberg P, *et al.* (1988). Incidence of organic dust toxic syndrome and allergic alveolitis in Swedish farmers. *Int Arch Allergy Appl Immunol*; 87: 47–54.
- Pepys J (1978). Antigens and hypersensitivity pneumonitis. *J Allergy Clin Immunol*; 61: 201–203.
- Salisbury ML, *et al.* (2017). Diagnosis and treatment of fibrotic hypersensitivity pneumonia where we stand and where we need to go. *Am J Respir Crit Care Med*; 196: 690–699.
- Solaymani-Dodaran M, *et al.* (2007). Extrinsic allergic alveolitis: incidence and mortality in the general population. *QJM*; 100: 233–237.
- Vasakova M, *et al.* (2017). Hypersensitivity pneumonitis: perspectives in diagnosis and management. *Am J Respir Crit Care Med*; 196: 680–689.

Sarcoidosis

Ulrich Costabel

Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology, which commonly affects young and middle-aged adults. The disease frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions. Any organ of the body may be involved. The prevalence rates of sarcoidosis vary widely, from <1 case to 40 cases per 100 000 population. Sarcoidosis is common in Scandinavia, Central Europe, the USA and Japan. It is less frequently seen in other Asian countries, Central and South America, and Africa. Sarcoidosis in African–Americans is more severe, while Caucasians are more likely to present with asymptomatic disease. Overall mortality is 1–5%.

The cause of sarcoidosis remains unknown. Available evidence strongly supports the hypothesis that the disease develops when a specific environmental exposure with antigenic properties occurs in a genetically susceptible individual. Potential aetiological agents include mycobacteria and *Propionibacterium acnes*. Sarcoidosis susceptibility or chronicity has been associated with a number of human leukocyte antigen alleles. Some genetic associations have been found with specific disease subsets, most notably with Löfgren syndrome. A polymorphism of the *BTNL2* (butyrophilin-like 2) gene has been linked with sarcoidosis. The immunological abnormalities are characterised by the accumulation of activated T-cells of the T-helper cell type 1 and macrophages at sites of ongoing inflammation.

Key points

- Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology, which commonly affects young and middle-aged adults.
- Prevalence of sarcoidosis varies from <1 case to 40 cases per 100 000 population, and overall mortality is 1–5%.
- Clinical presentation varies widely, though fever, fatigue and skeletal muscle weakness are often noted.
- The decision to treat should be carefully assessed based on the benefit to the patient and disease severity; treatment should mainly be considered if symptoms develop or lung function deteriorates.
- The clinical course of sarcoidosis can be unpredictable, so regular monitoring of signs of disease progression is advised.

Clinical presentation

The clinical presentation of sarcoidosis varies widely. 30–50% of patients are asymptomatic at the time of diagnosis. Symptoms of sarcoidosis are largely nonspecific. Low-grade fever (sometimes up to 40°C), weight loss (usually limited to 2–6 kg during the 10–12 weeks before presentation), night sweats and arthralgias can be found in about 20–30% of patients. Sarcoidosis is an important and frequently overlooked cause of fever of unknown origin. Fatigue is more common, being present in ≤70% of patients when carefully asked for. For the assessment of these general symptoms, the King's Sarcoidosis Questionnaire, a sarcoidosis-specific modular multiorgan health status measure, can be used in clinics and research. According to their initial presentation, sarcoidosis patients can be divided into two distinct subgroups: acute and chronic. The acute form can present as classical Löfgren syndrome, which is characterised by fever, bilateral hilar lymphadenopathy, ankle arthritis and erythema nodosum. The chronic form shows an insidious onset and organ-related symptoms predominate, such as cough, dyspnoea and chest pain.

Diagnostic approach

The criteria of the American Thoracic Society, European Respiratory Society and the World Association of Sarcoidosis and Other Granulomatous Disorders for the diagnosis of sarcoidosis include:

- the presence of a consistent clinical and radiological picture;
- histological evidence of noncaseating granulomas; and
- exclusion of other conditions capable of producing a similar histological or clinical picture.

The initial diagnostic work-up for patients with suspected sarcoidosis involves careful baseline assessment of disease distribution and severity by organ, with emphasis on vital target organs (table 1). Specifically, the diagnostic assessment should attempt to accomplish four goals:

- provide histological confirmation of the disease;
- assess the extent and severity of organ involvement;
- assess whether the disease is stable or is likely to process; and
- determine whether therapy will benefit a patient.

Table 1. Initial evaluation for sarcoidosis

History (occupational and environmental exposure, symptoms)
Physical examination
Chest radiography
Pulmonary function tests: vital capacity, FEV_1, T_{LCO}
Peripheral blood counts
Serum chemistries: calcium, liver enzymes, creatinine, ACE
Urine analysis
ECG
Eye investigation
Microbiological examination of specimen
Selection of site for biopsy

ACE: angiotensin-converting enzyme.

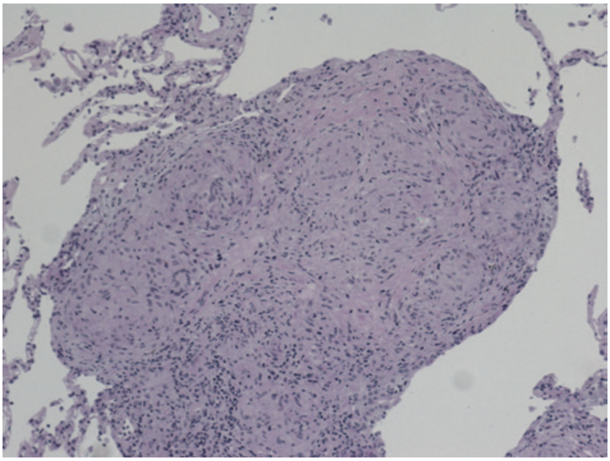


Figure 1. Transbronchial lung biopsy showing a noncaseating epithelioid cell granuloma with some Langerhans' giant cells in a patient with sarcoidosis. Courtesy of T. Hager (Institute of Pathology, University Hospital Essen, Essen, Germany).

Noncaseating epithelioid cell granulomas alone are never diagnostic proof of sarcoidosis.

An important step is the choice of site for a proper biopsy. Transbronchial lung biopsy is the recommended procedure in most cases, with the diagnostic yield reaching 80% (figure 1). This can be combined with biopsy of the bronchial mucosa. Transbronchial needle aspiration of mediastinal lymph nodes guided by endobronchial ultrasound is useful for diagnosing stage I and II sarcoidosis with a sensitivity of 83–93%. Other easily accessible sites for biopsy are the skin, lip or superficial lymph nodes.

In patients without biopsy, clinical and/or radiological features alone may be diagnostic in stage I (reliability of 98%) or stage II (89%), but are less accurate in stage III (52%) or stage 0 (23%). The classical Löfgren syndrome or the Heerfordt syndrome (uveitis, parotits, Bell's palsy and fever) may not require biopsy proof. Bronchoalveolar lavage and studies of lymphocyte subpopulations showing an increase in the CD4/CD8 ratio may be helpful. Elevated serum angiotensin-converting enzyme and calcium levels may lend support to the diagnosis.

The chest radiogram can be used to classify sarcoidosis into four stages (table 2). The lungs and thoracic lymph nodes are involved in 95–100% of patients. CT scanning provides much greater detail of mediastinal and parenchymal abnormalities but is not essential for baseline study. The characteristic findings of sarcoidosis on lung CT scans are small nodules with a bronchovascular and subpleural distribution, thickened

Table 2. Chest radiographic stages

Stage	Findings	Frequency %
0	Normal	5–10
I	BHL	50
II	BHL and parenchymal infiltrates	25
III	Parenchymal infiltrates without BHL	15
IB	Signs of fibrosis	5–10

BHL: bilateral hilar lymphadenopathy.

interlobular septa, architectural distortion and conglomerate masses (figure 2). It is indicated when diagnosis is unclear after chest radiography and clinical assessment or to detect complications of the lung disease including bronchiectasis, aspergilloma or superimposed infection. FDG-PET scanning can be of value to detect occult diagnostic biopsy sites and to assess reversible activity in selected patients.

Pulmonary function tests show only a moderate correlation with the extent of lung involvement detected on imaging. However, it is important to have initial baseline data for evaluating the following clinical course. The most sensitive test is the diffusion capacity. The typical finding is a restriction, but up to 30% of patients show an obstructive impairment that may be associated with the involvement of the airways. Bronchial hyperreactivity may be seen in up to 50% of patients.

Cardiac involvement is a serious manifestation of sarcoidosis. Cardiac MRI is the preferred diagnostic test as it is a noninvasive and nonradioactive method for diagnosing cardiac sarcoidosis with a high sensitivity.

Pulmonary hypertension is a troublesome complication of sarcoidosis, with increased morbidity and mortality. The frequency is 5–15% in unselected patients and 50–60% in patients with dyspnoea out of proportion with the pulmonary function test results. Such patients, most of them in radiographic stage IV, should undergo echocardiography as a screening test and right heart catheterisation for confirmation.

Natural history and prognosis

The disease course is highly variable. Spontaneous remissions occur in nearly two-thirds of patients. Serious extrapulmonary involvement (cardiac, central nervous system or hepatic) occurs in 4–7% of patients at time of presentation. Incidence becomes higher as the disease evolves. Adverse prognostic factors include lupus pernio, chronic uveitis, age at onset >40 years, chronic hypercalcaemia, nephrocalcinosis, African ethnic origin, progressive pulmonary sarcoidosis, nasal mucosal involvement, cystic bone lesions, neural sarcoidosis, cardiac sarcoidosis, pulmonary hypertension and chronic respiratory insufficiency.

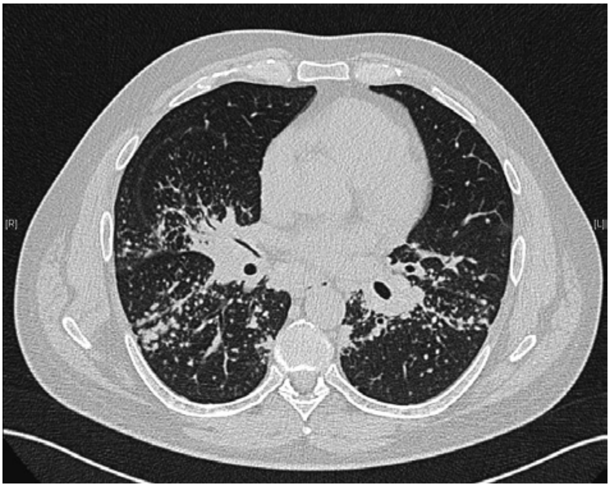


Figure 2. HRCT in sarcoidosis showing the characteristic micronodules predominantly along the bronchovascular bundles (lymphangitic distribution pattern).

Treatment and follow-up

The indication to treat a patient depends on many factors, the most important being whether or not the patients is symptomatic. Except for life- and sight-threatening organ involvement, it should be carefully considered whether the patient might benefit from treatment. For asymptomatic pulmonary patients, a watch-and-wait approach is appropriate; treatment should mainly be considered if symptoms develop or lung function deteriorates. The goal of treatment is to make the patient asymptomatic and to restore or preserve organ function.

For patients with symptoms from a single organ, topical therapy may be appropriate for anterior eye or skin involvement and for bronchial hyperreactivity. Otherwise, initial therapy is still based on systemic corticosteroids. For pulmonary sarcoidosis, the initial prednisone dose is 20–40 mg; higher doses may be needed for cardiac or neural sarcoidosis. The dose is slowly tapered to 5–10 mg per day usually within 3 months; treatment should be continued for a minimum of 12 months. Patients with Löfgren syndrome usually do not require therapy with corticosteroids.

For patients with chronic disease requiring years of therapy, corticosteroid-sparing immunosuppressants include methotrexate, azathioprine and hydroxychloroquine, all usually given in combination with low-dose corticosteroids. For refractory sarcoidosis patients, new therapeutic approaches have begun to emerge through the use of immunomodulatory agents. Based on current understanding of pathogenic mechanisms, these are tumour necrosis factor-α-blocking drugs, such as infliximab, thalidomide and pentoxyfylline. Lung transplantation can be considered for severe or end-stage pulmonary sarcoidosis.

Because the clinical course of sarcoidosis can be unpredictable, regular monitoring for signs of disease progression is necessary, using the least invasive and most sensitive tools. For pulmonary sarcoidosis, this is spirometry and diffusion capacity. For stable stage I disease, follow-up every 6–12 months is usually adequate; more frequent evaluations (every 3–6 months) are advised for stage II, III or IV sarcoidosis. All patients should be monitored for a minimum of 3 years after therapy is discontinued. Follow-up needs to be more vigilant after corticosteroid-induced remissions, due to the high rate of relapses in this context, ranging 15–70%.

Further reading

- Baughman RP, *et al.* (2013). Established and experimental medical therapy of pulmonary sarcoidosis. *Eur Respir J*; 41: 1424–1438.
- Birnie DH, *et al.* (2014). HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm*; 11: 1305–1323.
- Costabel U, *et al.* (2010). Diagnostic modalities in sarcoidosis: BAL, EBUS, and PET. *Semin Respir Crit Care Med*; 31: 404–408.
- Drent M, *et al.*, eds. (2005). Sarcoidosis. ERS Monograph. Sheffield, European Respiratory Society.
- Hunninghake GW, *et al.* (1999). ATS/ERS/WASOG statement on sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*; 16: 149–173.
- Valeyre D, *et al.* (2014). Sarcoidosis. *Lancet*; 383: 1155–1167.
- Vorselaars ADM, *et al.* (2013). Methotrexate *vs* azathioprine in second-line therapy of sarcoidosis. *Chest*; 144: 805–812.
- Wessendorf TE, *et al.* (2015). Diagnosis of sarcoidosis. *Clin Rev Allergy Immunol*; 49: 54–62.

Idiopathic interstitial pneumonias

Marina Aiello, Alberto Fantin, Panayota Tzani, Sara Chiesa and Dario Olivieri

Idiopathic interstitial pneumonias (IIPs) represent a heterogeneous group of disorders among interstitial lung diseases (ILDs), with different clinical and histological features. They can be considered as inflammatory disorders of the interstitium. Extrapulmonary involvement does not occur. The cause and pathogenetic mechanisms responsible for IIPs have not been elucidated. The first stage of the pathological process consists of the recruitment of inflammatory cells in the interstitium, leading to injury of the epithelial and alveolar cells, and the subsequent abnormal wound healing response, particularly due to the fibroblasts. Nowadays, the dysregulation of fibroblasts and an excessive deposition of extracellular matrix are considered the cardinal points of the pathogenesis of IIPs.

Because of the poor comprehension of the underlying pathogenetic mechanisms, no therapeutic intervention is able to affect the cellular and molecular target responsible for the disease and change its course.

The most recent American Thoracic Society (ATS) and European Respiratory Society (ERS) classification of the IIPs, published in 2013, includes different diseases, divided into major, rare and unclassifiable ones (table 1).

Each entity is related to both a typical radiological and histological pattern; possessing a specific, sometimes variable prognostic horizon.

Here, we discuss the most important clinical aspects of the IIPs, particularly therapeutic possibilities.

Epidemiology

The incidence of the IIPs has been estimated at seven to 11 cases per 100 000 persons and the prevalence ranges between two and 29 cases per 100 000 persons.

Key points

- Idiopathic interstitial pneumonias represent a heterogeneous group of disorders with different clinical and histological features and prognoses.
- The most recent American Thoracic Society and European Respiratory Society classification of the idiopathic interstitial pneumonias includes different diseases, divided into major, rare and unclassifiable diseases.
- The terms idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia should only be used for chronic fibrosing interstitial pneumonia of unknown cause limited to the lungs. The prognosis in idiopathic pulmonary fibrosis is worse with a histological pattern of usual interstitial pneumonia.

Table 1. Classification of IIPs

Major IIP

- Idiopathic pulmonary fibrosis
- Idiopathic nonspecific interstitial pneumonia
- Respiratory bronchiolitis–interstitial lung disease
- Desquamative interstitial pneumonia
- Cryptogenic organising pneumonia
- Acute interstitial pneumonia

Rare IIP

- Idiopathic lymphoid interstitial pneumonia
- Idiopathic pleuroparenchymal fibroelastosis

Unclassifiable IIP

The disease typically affects adults, with a peak after the sixth decade of life, and incidence is higher in men and in smokers (Coultas *et al*., 1994). There are familial variants of idiopathic pulmonary fibrosis (IPF), accounting for 2–20% of cases. These forms are indistinguishable from the nonfamilial ones on HRCT and biopsy specimen, except that patients tend to be younger.

Pathogenesis

The pathogenetic mechanisms of the IIPs are not completely clear; there are various hypotheses relating to the initial stimulus responsible for the pathogenetic process, such as exposure to toxic substances or viral infections. Independently of the initial cause, the inflammatory–fibrotic process of usual interstitial pneumonia (UIP) is characterised by an injury of the alveolar epithelial cells, destruction of the subepithelial basement membrane, subsequent abnormal cicatrisation with an increased fibroblastic response, and excessive deposition of collagen and extracellular matrix.

The interplay between inflammatory and mesenchymal cells is regulated by a number of cytokines produced by fibroblasts and epithelial cells; the most important of these mediators are transforming growth factor (TGF)-β, tumour necrosis factor (TNF)-α, platelet-derived growth factor (PDGF), connective tissue growth factor, integrin-mediated intercellular adhesion molecules, proteases and oxygen radicals. Deficiency of interferon (IFN)-γ may contribute to activation and perpetuation of the fibroblastic process. Histologically, the presence of fibroblastic foci is typical of UIP; the fibroblastic foci are formed by mesenchymal cells similar to myofibroblasts. Under the influence of TGF-β, the cells increase the production of collagen, vimentin and actin, leading to an excessive deposition of extracellular matrix.

In the rare familial form, the mode of transmission is not known; an autosomal dominant modality has been proposed with variable penetrance in two-thirds of patients. Familial interstitial pneumonia has been associated with altered α_1-antitrypsin inhibitor alleles on chromosome 14 and heterozygous mutations in SFTPC, SFTPA2, TERT and TERC genes. In addition, genetic polymorphism for interleukin (IL)-1 receptor antagonist or TNF-α may be involved. Furthermore, genome-wide analysis showed a link between a variant in the promoter of the MUCB gene and both familial and sporadic IPF (Richeldi *et al*., 2017).

Physiology

The physiological aberrations in IIPs are typical of a restrictive pattern and include reduced lung volumes (vital capacity and TLC) and normal or increased expiratory flow rates. Lung function impairment at baseline and at subsequent follow-up is closely linked to patient prognosis.

T_{LCO} is typically reduced, with associated increased alveolar–arterial oxygen tension difference, indicating interstitium damage and, thereby gas exchange impairment (Chetta *et al*., 2004). In addition, progressive fibrosis leads to reduced lung compliance and increased recoil pressures, producing a shallow and rapid breathing pattern, with an increase in dead space ventilation. A further consequence of these alterations is hypoxaemia, which is usually accentuated by exercise. Factors that worsen this condition are the disproportionate rise in pulmonary vascular resistance and pulmonary hypertension in a subset of patients with IIPs. Late in the course of the disease, severe hypoxaemia may also be observed at rest; hypercapnia may be present as well and is a feature of end-stage disease.

Clinical features and diagnosis

The initial symptoms of IIPs are hidden and insidious: persistent nonproductive cough and progressive dyspnoea. In most patients, physical examination reveals end-inspiratory rales (velcro type). The course of the disease may vary depending on the variant of IIP; in UIP, the prognosis is extremely severe and the course of the disease is rapid, even if some patients stabilise after an initial period of clinical decline. Respiratory failure appears within 3–8 years and mean survival from the onset of the disease is around 3 to 5 years. During the late phases of the disease, patients often show cor pulmonale. Respiratory failure is the main cause of death, followed by pulmonary embolism and heart failure.

The diagnosis of IIP is the result of an integrated and multidisciplinary process, requiring cooperation from the clinician, radiologist and pathologist (Tomasetti *et al*., 2017). International ATS/ERS/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAS) guidelines, published in 2018, underline how HRCT is the core diagnostic protocol (table 2). In fact, it has become a crucial tool for the diagnostic process and allows an accurate and objective follow-up of the disease. Imaging features are often typical of the disease and, given the high-quality evidence regarding HRCT specificity for the recognition of a histopathological UIP pattern, surgical lung biopsy is not always mandatory (figure 1). IPF is diagnosed by identification of a UIP pattern based on radiological or histological criteria, in patients without evidence of an alternative cause. A clinical checklist for alternative diagnosis has already been proposed (Lynch *et al*., 2018).

In the case of UIP, HRCT images show a heterogeneous distribution of lesions with a predilection for the peripheral, especially subpleural and basilar regions of the lung. The main radiologic feature in UIP is honeycombing, *i.e.* clustered cystic spaces, as an expression of severe and irreversible fibrotic conversion of the parenchyma. Secondary features include coarse reticular opacities, traction bronchiectasis or bronchiolectasis. In the right clinical context, the diagnosis can be confirmed by HRCT alone in cases with a typical UIP pattern; additional tests are needed for findings of probable, indeterminate UIP and when alternative diagnosis are considered. Nevertheless, the patient must be followed over time since, as with any IIP, the diagnosis may change later. Serological testing to exclude connective tissue disease-ILDs are recommended.

Table 2. HRCT scanning patterns

UIP pattern	Probable UIP pattern	Indeterminate pattern	Alternative diagnosis
Subpleural and basal predominant; distribution is often heterogeneous[#]	Subpleural and basal predominant; distribution is often heterogeneous	Subpleural and basal predominant	Findings suggestive of another diagnosis, including: CT features: cysts, marked mosaic attenuation, predominant GGO, profuse micronodules, centrilobular nodules, nodules, consolidation
Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis[¶]	Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis	Subtle reticulation; may have mild GGO or distortion (early UIP pattern)	Predominant distribution: peribronchovascular, perilymphatic, upper or mid-lung
	May have mild GGO	CT features and/or distribution of lung fibrosis that do not suggest any specific aetiology (truly indeterminate)	Other: pleural plaques (consider asbestosis), dilated oesophagus (consider CTD), distal clavicular erosions (consider RA), extensive lymph node enlargement (consider other aetiologies), pleural effusions, pleural thickening (consider CTD/drugs)

GGO: ground-glass opacities; CTD: connective tissue disease; RA: rheumatoid arthritis. [#]: variants of distribution: occasionally diffuse, may be asymmetrical; [¶]: superimposed CT features: mild GGO, reticular pattern, pulmonary ossification. Reproduced from Raghu *et al.* (2018) with permission from the publisher.

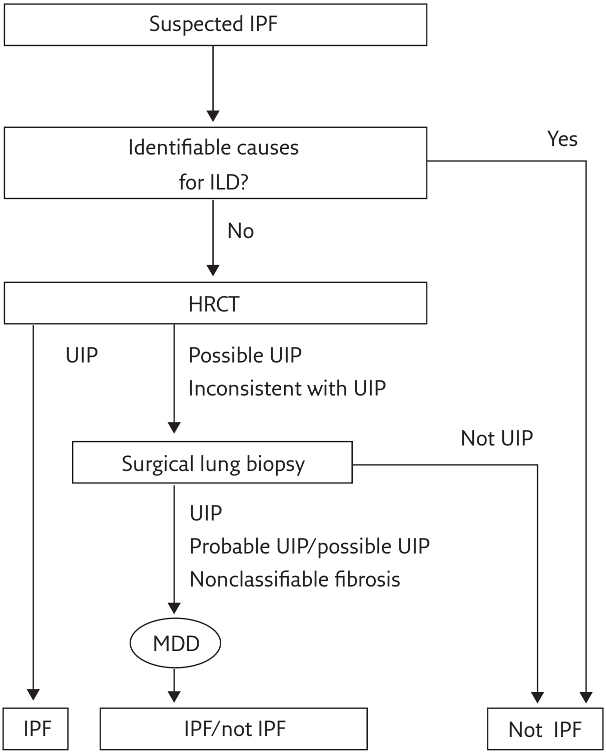

Suspected IPF
Identifiable causes for ILD?
Yes
No
HRCT
UIP
Possible UIP
Inconsistent with UIP
Surgical lung biopsy
Not UIP
UIP
Probable UIP/possible UIP
Nonclassifiable fibrosis
MDD
IPF
IPF/not IPF
Not IPF

Figure 1. Diagnostic algorithm for IPF. ILD: interstitial lung disease; MMD: multidisciplinary discussion. Reproduced and modified from Raghu et al. *(2011) with permission from the publisher.*

Surgical lung biopsy by video-assisted thoracoscopic surgery remains useful and shows higher diagnostic value than transbronchial biopsy and bronchoalveolar lavage. However, the guidelines advise against an invasive sampling if a pattern of UIP is detected (Raghu *et al*., 2018). Recently, some interventional pulmonology techniques have been adopted in order to improve the diagnostic result in IPF. Despite the guidelines not providing favourable recommendations for its application in cases where biopsy is required, a method that merits mention is cryobiopsy, which is presently performed in highly specialised centres.

Nonspecific interstitial pneumonia (NSIP) is characterised by the presence of ground-glass areas, as a sign of active inflammatory process. The main aspects to consider for the differential diagnosis between UIP and NSIP are the geographic and temporal histological and radiological heterogeneity, the high concentration of fibroblastic foci and honeycombing in the UIP form.

Cellular analyses of bronchoalveolar lavage (BAL) and transbronchial lung biopsy can be useful in the diagnosis of certain rare forms of IIPs (Meyer *et al*., 2012).

Natural history and exacerbations

The course of the disease is characterised by a progressive decline in pulmonary function, leading to worsening of general condition and death (figure 2).

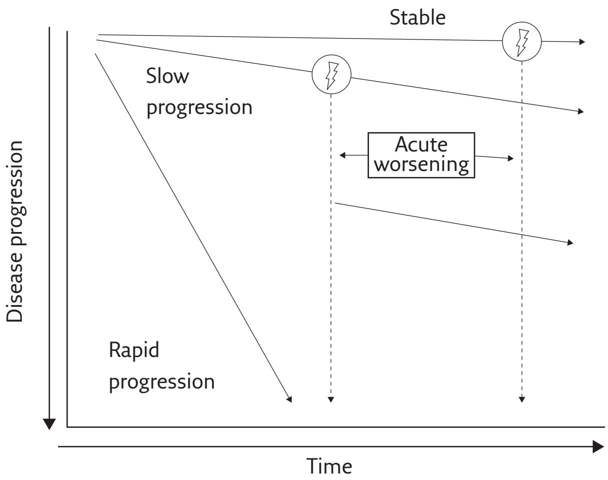


Figure 2. Natural history of IPF. Reproduced from Raghu et al. *(2011), with permission from the publisher.*

IPF is the IIP studied most in the literature. It is known that a subset of patients with IPF develop an accelerated and usually fatal course, showing an extremely rapid decline in lung function. An acute, clinically significant respiratory deterioration, characterised by evidence of new widespread alveolar abnormality defines an acute IPF exacerbation.

The diagnostic criteria for an acute exacerbation of IPF are:

- previous or concurrent diagnosis of IPF;
- acute worsening or development of dyspnoea typically <1 month in duration;
- CT with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with UIP pattern;
- deterioration not fully explained by cardiac failure or fluid overload.

The diagnosis of an exacerbation may be controversial, despite the codification of the diagnostic criteria, as ground-glass opacities are not specific for IIPs and may be present in infection. Nonintubated patients in the acute phase of the disease often cannot undergo BAL because of their unstable conditions and they are treated empirically with antibiotics as a precautionary measure or with high-dose steroid therapy.

Lung biopsy shows diffuse alveolar damage; however, the invasiveness of the procedure is a limiting factor and should be avoided due to its high morbidity in this setting. It is our duty to mention the correlation between surgical lung biopsy or lung resection and acute exacerbation, which is not clear yet as far as causality is concerned. Risk factors involved in this accelerated phase may be a high concentration of oxygen (100%), hyperexpansion of the lung parenchyma and the use of mechanical ventilation in the post-operative phase.

Generally, the factors responsible for the exacerbations are still unknown; clinical presentation in some patients (fever, influenza-like symptoms and neutrophilia in BAL) may be consistent with a viral infection; however, the pathogen has not yet been identified.

Treatment

IIP treatment is one of the most controversial aspects in the field of diffuse infiltrative lung diseases. Poor understanding of the pathogenetic mechanisms underlies the ineffectiveness of the current treatment options.

The initial pathogenetic theory considering IIPs as an inflammatory process makes the use of anti-inflammatory drugs reasonable, such as corticosteroids, which are considered first-line therapy. Later, cytotoxic and immunosuppressive agents have been used, usually in combination with corticosteroids.

The most recent developments in the field identify the initial phase of the disease as an alveolar epithelial cell injury with associated destruction of the subepithelial basement membrane, leading to abnormal wound healing with a vigorous fibroblastic response and excessive deposition of collagen and extracellular matrix. This new pathogenetic theory suggests a primary role for fibroblast dysregulation. Thus, the fibroproliferative process becomes the therapeutic target, and new drugs that arrest the proliferation of fibroblasts and the deposition of extracellular matrix are being tested.

The increasing clinical awareness of IPF has resulted in the publication of guidelines for its accurate diagnosis and recommendations for its management. The updated recommendations for diagnosis and treatment intervention in the 2018 ATS/ERS/JRS/ALAT guidelines are evidence-based and eliminate the bias from expert opinions and ongoing practices in the management of IPF.

Anti-inflammatory drugs

Although corticosteroids have been considered the mainstay of IPF treatment for decades, there are no randomised placebo-controlled trials using corticosteroids alone. The ATS/ERS international consensus statement concludes that existing therapies of this kind are of unproven benefit.

In the past, high doses of prednisone or prednisolone (1 $mg \cdot kg^{-1} \cdot day^{-1}$, considering ideal body weight) for 4 to 6 weeks, with a gradual taper, were used. Given the high risk of systemic side-effects and the significant toxicity, especially when used in combination with other drugs, the dose has been re-evaluated and more recent therapeutic regimens recommend low doses of prednisone or prednisolone (0.5 $mg \cdot kg^{-1} \cdot day^{-1}$ for 4 weeks followed by 0.25 $mg \cdot kg^{-1} \cdot day^{-1}$ for 8 weeks, then 0.125 $mg \cdot kg^{-1} \cdot day^{-1}$). The rate of taper depends on patients' individual characteristics. In the case of clinical and radiological responders, prolonged maintenance therapy with low-dose, alternate-day prednisone may be established to reduce the chance of revival in active disease. In the case of a subsequent exacerbation, 2 $mg \cdot kg^{-1} \cdot day^{-1}$ of methylprednisolone for approximately 14 days should be administered, depending on individual clinical response.

Given the lack of any scientific evidence of proven benefit, especially a dose–response effect, corticosteroid treatment should not be used in patients at high risk for adverse effects, such as elderly patients.

When the inflammatory component dominates, prompt corticosteroid treatment may lead to a significant improvement and, sometimes, to complete resolution of the disease. Desquamative interstitial pneumonia, acute interstitial pneumonia and cryptogenic organising pneumonia are the forms of IIP with the highest rate of response to steroid therapy.

The guidelines recommend that patients with IPF should not be treated with corticosteroid monotherapy.

Azathioprine and cyclophosphamide are the most frequently used second-line drugs, alone or in combination with corticosteroids. Currently, there is poor information regarding their efficacy. A possibly adjunctive synergic effect is unconfirmed as well.

Azathioprine is the most frequently used cytotoxic agent and is usually well-tolerated. Its metabolism leads to the production of mercaptopurine, which is similar to purine, and inhibits DNA synthesis. Azathioprine is administered orally, usually in combination with low-dose corticosteroids; the initial dose is 25–50 $mg \cdot day^{-1}$ (2–3 $mg \cdot kg^{-1} \cdot day^{-1}$). If adverse effects do not appear, an increase of 25 mg every 7–14 days is recommended, until a maximum dose of 150 $mg \cdot day^{-1}$ is reached. During treatment with azathioprine, blood cell count and liver function should be monitored; in fact, azathioprine causes bone marrow suppression and hepatotoxicity. There are no clinical trials that confirm a certain benefit of combination (corticosteroids plus azathioprine) therapy. Given the minor toxicity compared with cyclophosphamide, azathioprine should be administered in patients with symptomatic or progressive disease for 6 months unless adverse effects that suggest interruption or modification of the treatment appear. A more prolonged treatment is reserved only in patients with a clinical response or complete remission of the disease.

Cyclophosphamide is usually used as a second-line drug for patients who presented adverse effects from high-dose corticosteroid therapy. It is an alkylating agent that activates the liver microsomal system and inhibits DNA synthesis; it has a marked effect on lymphocytes; thus, it is used as an immunosuppressive agent. The route of administration is usually oral or intravenous but it can also be administered by intramuscular injection. Generally, cyclophosphamide is used in combination with low-dose corticosteroids. Principal adverse effects are bone marrow suppression, haemorrhagic cystitis, nausea and vomiting. Scientific evidence confirming the efficacy of cyclophosphamide in IIP treatment is lacking; no clinical benefit regarding survival and progression of the disease has been reported.

Cyclosporine is a fungal peptide that exerts potent immunosuppressive effects; it inhibits T-lymphocyte proliferation by inhibiting the release of interleukin-2. It causes some important adverse effects, especially renal, hepatic and gastrointestinal. Cyclosporine is rarely used for IIP treatment and its use is limited to selected patients awaiting lung transplantation. There are no clinical trials showing that cyclosporine therapy is of benefit. The new guidelines recommend that patients with IPF should not be treated with cyclosporine. Moreover, combination therapy with corticosteroid and immunomodulator therapy should not be recommended in IPF patients.

Novel therapeutic strategies

The use of novel drugs in IIP treatment is suggested by the new pathophysiological theory that recognises the fibroproliferative process plays a central role.

IFN-γ is a biological antifibrotic drug with a number of inhibitory effects on fibroblasts. In the literature, there are only a few studies relating to the real efficacy of IFN-γ, either alone or in combination therapy with low-dose corticosteroids. No study has shown any statistically significant differences in the primary outcome variables, such as disease progression, mortality and functional deterioration. However, patients with mild-to-moderate disease presented better, statistically significant survival. Although IFN-γ may represent a useful therapeutic tool in selected patients, additional data supporting its efficacy are needed. The new guidelines recommend that patients with IPF should not be treated with IFN-γ.

Colchicine inhibits the synthesis of collagen and suppresses some growth factors that are necessary for fibroblast proliferation. On the basis of these properties, the use of this drug is being tested. Data are limited, although there is no evidence that colchicine improves the progression of the disease and survival. The new guidelines recommend that patients with IPF should not be treated with colchicine.

D-penicillamine is a thiolic compound that interferes with collagen turnover, inhibiting collagen synthesis and deposition by interrupting cross-linking of collagen molecules. There are no clinical controlled trials showing any benefit of D-penicillamine therapy. Given the frequency of adverse effects, D-penicillamine does not appear to be a treatment choice in IIPs.

Pirfenidone (5-methyl-1-phenyl-2[1H]-pyridone) attenuates pulmonary fibrosis in animal models. It reduces synthesis of collagen (I and III) and TNF-α, and inhibits TGF-β-stimulated collagen synthesis. Moreover, it decreases synthesis of extracellular matrix and blocks the mitogenic effect of profibrotic cytokines. Azuma *et al.* (2005) published the results of a double-blind, randomised, placebo-controlled trial but no statistically significant difference in desaturation during the 6-min walk test (6MWT) was found; however, a positive treatment effect with pirfenidone was demonstrated in secondary end-points, such as vital capacity and prevention of acute exacerbation of the disease. In fact, successive trials (CAPACITY and ASCEND) showed that pirfenidone preserves vital capacity and improves progression-free survival time better than placebo. On the contrary, patients treated with pirfenidone were more likely to experience photosensitivity, fatigue dyspepsia and anorexia. The new guidelines recommend pirfenidone for patients with IPF.

Experimental models *in vitro* and *in vivo* showed that angiotensin-converting enzyme inhibitors and statins possess antifibrotic properties. However, there is no evidence of survival improvement in treated patients.

There is evidence that oxidant agents production increases in IIP. In particular, neutrophils, macrophages and fibroblasts release oxidant agents, such as reactive oxygen species, hydrogen peroxide and superoxide anions. These factors, added to the reduction of antioxidants, facilitate fibroblast dysregulation and deposition of extracellular matrix. N-acetylcysteine (NAC) is derived from the amino acid cysteine. It is considered a precursor of glutathione (GSH) and stimulates GSH synthesis. GSH has strong antioxidant properties as it removes free oxygen radicals and decreases hydrogen peroxide. NAC monotherapy has not showed advantages in terms of FVC change in two randomised controlled trials (Martinez *et al*., 2014), so it is not recommended.

In one study increased risks of death and hospitalisation were observed in patients with IPF who were treated with a combination of prednisone, azathioprine and NAC, compared with placebo. The new guidelines strongly recommend that patients should not be treated with NAC monotherapy or with combination corticosteroid, azathioprine and NAC therapy, but this therapy may be reasonable in a minority of patients.

Endothelin 1 (ET-1) is a potent mitogen for endothelial and smooth muscle cells. ET-1 is strongly upregulated in patients with IIP and is mainly expressed in epithelial cells. Some studies have suggested that inhibition of ET-1 could have antifibrotic effects. Bosentan is a nonselective ET_A and ET_B receptor antagonist which is used in patients with pulmonary hypertension, and it could delay the progression of IIPs. The BUILD (Bosentan Use in Interstitial Lung Disease)-1 trial showed that bosentan was not superior to placebo in the 6MWT, and the effects of bosentan treatment on health-related quality of life and dyspnoea in the all-treated population were minimal. Similarly, in the BUILD-3 trial, no treatment effects were observed on health-related quality of life or dyspnoea.

Ambrisentan, a selective endothelin receptor antagonist, showed an increase in disease progression by associating with T_{LCO} and FVC decline.

Macitentan, a brand new dual receptor endothelin receptor antagonist, did not show any advantages in terms of mortality or FVC decline. The combined guidelines' recommendation for these antagonists is against their use in IPF patients.

Sildenafil, a phosphodiesterase-5 inhibitor, has been evaluated in the STEP-IPF trial and did not show significant improvement in the 6-min walking distance (6MWD), but improved dyspnoea, quality of life, T_{LCO} and arterial oxygen saturation. A subsequent subgroup analysis, investigating patients affected by right ventricular systolic dysfunction, demonstrated a significant improvement in terms of 6MWD. Despite the findings, sildenafil use is currently not suggested by the guidelines.

TNF-α has been found to be significantly elevated in bleomycin-induced pulmonary fibrosis. TNF-α stimulates a series of cytokines, such as TGF-β and interleukin-5, and modifies eosinophil recruitment in the parenchyma. Antibodies against TNF-α and soluble TNF-α receptor antagonists have been found to reduce the fibrotic process in animals. A study of etanercept for patients with IPF failed to show a difference in the primary end-point of change in FVC. Nonsignificant trends were observed in T_{LCO} and 6MWT parameters. The guidelines recommend that patients with IPF should not be treated with etanercept.

Tyrosine kinase receptors have been shown to be involved in lung fibrosis. Imatinib, a tyrosine kinase inhibitor, is currently not recommended by the guidelines due to costs, associated adverse events and ineffectiveness in the context of survival and disease progression in a randomised controlled trial.

Nintedanib is a potent intracellular inhibitor of tyrosine kinases; its targets include PDGF-α and -β receptors, vascular endothelial growth factor receptors 1–3, and fibroblast growth factor receptors 1–3. Three randomised controlled trials regarding patients affected by IPF showed evidence that a dose of 150 mg twice daily was associated with a reduction in the decline in lung function, fewer acute exacerbations and preserved quality of life (Richeldi *et al.*, 2011; Richeldi *et al.*, 2014). Unfortunately they did not show survival benefits and the available evidence is limited to patients with mild-to-moderate impairment in pulmonary function tests.

The typical fibroproliferative process in IIP seem to be related to inflammation and vascular injury. Indeed, endothelium damage causes exposition of the intimal tissue to the circulation and this is strongly pro-thrombotic. Pulmonary embolism is one of the most common causes of death in IIP patients and D-dimer levels often increase in exacerbations of the disease. Certainly, extravascular deposition of fibrin and thrombotic events play a main role in the fibroproliferative process and acute lung injury. However, one randomised controlled trial (Noth *et al.*, 2012) comparing oral warfarin to placebo was stopped early due to a lack of benefit and potential harm with treatment. The new guidelines recommend strongly against treatment with anticoagulants in patients who do not have a known alternative indication for its use.

The study by Lee *et al.* (2011) showed an apparent survival benefit associated with medications to suppress the acidity of the gastric juice, given as gastro-oesophageal reflux (GOR) therapy. In an aggregate analysis of three randomised controlled trials, Lee *et al.* (2013) showed a slower decrease in FVC and less acute exacerbations in the treated group, compared to placebo. These observations are consistent with an increasing body of evidence supporting the concept of silent microaspiration as a result of abnormal GOR in the pathogenesis of IPF. If GOR therapy improves survival in patients with IPF, then even other interventions to decrease and control GOR should be implemented such as diet, sleep habits/behavioural patterns, decrease in abdominal girth, and laparoscopic anti-reflux surgery. However, further studies are needed to confirm these suggestions.

Oxygen therapy is still a debated matter in IIPs. Although exercise capacity seems to be increased during oxygen administration, no effect on dyspnoea has been found. There are still many evidences to be explored and researched about this topic (Bell *et al*., 2017).

Lung transplantation

Lung transplantation is the only option which definitely improves survival in IIP patients and the only option for patients refractory to medical therapy. IIPs represent one of the most frequent diseases that require lung transplantation. It is extremely important to decide when to list a patient for intervention. Given the legal complexity of the process, early listing is urged.

The International Society for Heart and Lung Transplantation published a consensus document for establishing the characteristics and criteria for referral to a lung transplant programme and active listing (table 3). The document recommends that appropriate patients affected by ILDs should undergo lung transplantation.

Table 3. International Society for Heart and Lung Transplantation Consensus; timing for lung transplant in ILDs

Timing of referral

- Histopathologic or radiographic evidence of UIP or fibrosing NSIP, regardless of lung function
- Abnormal lung function: FVC <80% pred or T_{LCO} <40% pred
- Any dyspnoea or functional limitation attributable to lung disease
- Any oxygen requirement, even if only during exertion
- For inflammatory ILD, failure to improve dyspnoea, oxygen requirement and/or lung function after a clinically indicated trial of medical therapy

Timing of listing

- Decline in FVC ≥10% during 6 months of follow-up (note: a 5% decline is associated with a poorer prognosis and may warrant listing)
- Decline in T_{LCO} ≥15% during 6 months of follow-up
- Desaturation to <88% or distance <250 m on 6-min walk test or >50 m decline in 6-min walk distance over a 6-month period
- Pulmonary hypertension on right heart catheterisation or two-dimensional echocardiography
- Hospitalisation because of respiratory decline, pneumothorax or acute exacerbation

Evidence to favour bilateral lung transplantation *versus* single lung transplantation is still lacking. In previous observational studies no significant difference in terms of survival was highlighted between the two techniques.

Unfortunately, many patients die while awaiting transplantation because of the poor availability of donor organs. Post-operative mortality in transplanted patients remains high because of rejection, infections and other complications. 2- and 5-year survival rates following single lung transplantation are ~70% and ~50%, respectively.

Stem cell-based therapy

Given the recent advances in IPF pathogenesis, new therapeutic models are being investigated, focusing on the cellular and molecular mechanisms underlying the disease. In particular, alveolar epithelial cell injury arises from an abnormal accumulation of fibroblasts and deposition of extracellular matrix, resulting in distortion of lung parenchyma architecture. Therefore, lung tissue regeneration, remodelling and repair mechanisms could represent new potential therapeutic targets.

The discovery that stem cells can contribute to the formation of differentiated cell types, especially after injury, justifies the experimental use of stem cells in tissue regeneration. It is believed that stem cells play a central role in cell injury and the fibrotic process; however, their role is still controversial. In particular, the mechanisms of cell recruitment to site in the case of tissue damage are not completely clear. Therefore, embryo or adult stem cell transplantation could be a valid novel therapeutic option in pulmonary fibrosis. Official data confirming the efficacy and applicability of this treatment are lacking; furthermore, the importance of immunosuppressive therapy before stem cells transplantation is unclear, as the data are poor.

End-of-life care

A large proportion of patients with IPF die in hospital, often while receiving advanced therapies. Palliative care for these patients has become a more relevant topic than ever before. Advanced directives should be collected early in the course of the disease to better address the patient's needs and immediately know the person's future wishes.

Further reading

- Azuma A, *et al.* (2005). Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*; 171: 1040–1047.
- Bell EC, *et al.* (2017). Oxygen therapy for interstitial lung disease: a systematic review. *Eur Respir Rev*; 26: 160080.
- Chetta A, *et al.* (2004). Pulmonary function testing in interstitial lung diseases. *Respiration*; 71: 209–213.
- Collard HR, *et al.* (2016). Acute exacerbation of idiopathic pulmonary fibrosis. An International Working Group Report. *Am J Respir Crit Care Med*; 194: 265–275.
- Coultas DB, *et al.* (1994). The epidemiology of interstitial lung diseases. *Am J Respir Crit Care Med*; 150: 967–972.
- Lee JS, *et al.* (2011). Gastroesophageal reflux therapy is associated with longer survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*; 184: 1390–1394.
- Lee JS, *et al.* (2013). Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomised controlled trials. *Lancet Respir Med*; 1: 369–376.

- Lynch DA, *et al.* (2018). Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. *Lancet Respir Med*; 6: 138–153.
- Martinez FJ, *et al.* (2014). Idiopathic Pulmonary Fibrosis Clinical Research Network: randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med*; 370: 2093–2101.
- Meyer KC, *et al.* (2012). An Official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med*; 185: 1004–1014.
- Noth I, *et al.* (2012). A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*; 186: 88–95.
- Raghu G, *et al.* (2011). An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*; 183: 788–824.
- Raghu G, *et al.* (2015). An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 Clinical Practice Guideline. *Am J Respir Crit Care Med*; 192: e3–e19.
- Raghu G, *et al.* (2018). Diagnosis of idiopathic pulmonary fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med*; 198: e44–e68.
- Richeldi L, *et al.* (2011). Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med*; 365: 1079–1087.
- Richeldi L, *et al.* (2014). Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*; 370: 2071–2082.
- Richeldi L, *et al.* (2017). Idiopathic pulmonary fibrosis. *Lancet*; 389: 1941–1952.
- Tomassetti S, *et al.* (2017). Diffuse parenchymal lung disease. *Eur Respir Rev*; 26: 170004.
- Travis WD, *et al.* (2013). An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*; 188: 733–748.
- Weill D, *et al.* (2015). A consensus document for the selection of lung transplant candidates: 2014 – an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*; 34: 1–15.

Adult pulmonary Langerhans cell histiocytosis

Vincent Cottin, Mouhamad Nasser, Claudia Valenzuela and Romain Lazor

Langerhans cells are bone marrow-derived antigen-presenting dendritic cells. Langerhans cell histiocytosis (LCH) belongs to a spectrum of rare systemic granulomatous disorders characterised by aberrant accumulation of histiocytes in various organs, which include LCH, non-Langerhans histiocytoses such as Erdheim–Chester disease and Rosai–Dorfman disease, and malignant histiocytic disorders. Pulmonary LCH occurs in young adult smokers and is, in most cases, limited to the lungs with occasional involvement of bone, skin and the pituitary gland, whereas LCH in childhood is generally systemic or multifocal.

Epidemiology

Pulmonary LCH in adults is rare, with an estimated prevalence of fewer than one case per 200000 persons, although it represents 3–5% of diffuse parenchymal lung diseases in adults. It occurs in smokers in >95% of cases, of which a proportion are also cannabis users. It occurs with equal frequency in both sexes, with a peak incidence between 20 and 40 years of age.

Pathophysiology

Until recently, pulmonary LCH was considered as a reactive immune granulomatous reaction, with some controversy about the possible clonal nature of $CD1a^+$ cells, and discrepancies between studies in systemic LCH in children and pulmonary LCH in adults. In the last few years, somatic mutations of *BRAF* (especially the V600E

Key points

- Pulmonary Langerhans cell histiocytosis (LCH) occurs in adult smokers aged 20–40 years.
- Somatic mutations of *BRAF* and other genes resulting in constitutive activation of the mitogen-activated protein kinase (MAPK) pathway are frequent and are thought to be pathogenic.
- Diabetes insipidus and bone and skin lesions may occur in adults with pulmonary LCH.
- The combination of nodules, cavitating nodules and cysts with relative sparing of the lung bases is highly characteristic at HRCT.
- Sustained smoking cessation is essential and is associated with a reduced longitudinal lung function decline.
- Drug therapy using cladribine or MAPK inhibitors is under evaluation.

mutation) and other genes (*MAP2K1* and *NRAS*) resulting in constitutive activation of the mitogen-activated protein kinase (MAPK) pathway have been identified in both systemic and pulmonary LCH, and are now thought to play a key pathogenic role. How tobacco smoking contributes to the recruitment of Langerhans cell clones to the lung is incompletely understood.

Pathological features

Pulmonary LCH is characterised by granulomatous bronchiolocentric organisation of Langerhans cells associated with inflammatory cells including eosinophils. Granulomas are loosely formed and predominate in the wall of distal bronchioles. Tobacco-pigmented alveolar macrophages are often associated. Langerhans cells do not differ from their normal counterparts in tissues, exhibiting convoluted irregular nuclei. Progression of bronchiolocentric granulomatous lesions results in destruction of the bronchiolar wall, dilatation of the bronchiolar lumen to form cystic cavities and end-stage stellar fibrotic scars.

Langerhans cells are stained with anti-CD1a and anti-CD207 (langerin) antibodies but cytoplasmic expression of the S100 protein lacks specificity. Electron microscopy is no longer used. Expression of $\text{BRAF}^{\text{V600E}}$ assessed by immunohistochemistry is an effective method to screen for this mutation when lung tissue is available.

Clinical features

Respiratory manifestations leading to the diagnosis of pulmonary LCH are usually not specific, with cough (often overlooked in smokers), and progressive dyspnoea on exertion. Spontaneous pneumothorax, often recurrent, is the first manifestation in 10–20% of patients. The disease is discovered incidentally on routine chest imaging in the remaining cases. Fever, malaise, weight loss and sweats are present in 10–20% of cases. Lung auscultation is generally normal.

Pulmonary LCH occurs as single-organ involvement in the large majority of patients. However, involvement of other systems may be present and can be the first disease manifestation. These include well demarcated and osteolytic bone lesions (*e.g.* rib involvement with possible chest pain), hypothalamic–pituitary involvement resulting in diabetes insipidus (polyuria and polydipsia) and skin lesions.

Chest imaging

HRCT of the chest usually shows characteristic features in early disease with bilateral, symmetric, disseminated infracentimetric nodules, which may show cavitation and may spontaneously disappear. The cavitated nodules typically evolve to thick-walled then thin-walled cysts (figure 1). The cysts may then enlarge and become confluent, often with irregular shapes, and later with HRCT features resembling emphysema. The combination of nodules, cavitating nodules and cysts, with relative sparing of the lung bases, is highly characteristic of the disease. When present, ground-glass attenuation suggests the association of smoking-related interstitial lung disease. Nodules can be hypermetabolic on positron emission tomography–CT.

The differential diagnosis includes other multiple cystic lung diseases on imaging, especially Birt–Hogg–Dubé syndrome and spontaneous familial pneumothorax related to folliculin gene (*FLCN*) mutations, lymphangioleiomyomatosis, Sjögren's syndrome and nonamyloid immunoglobulin deposition disease. Pleural effusion and mediastinal lymphadenopathy are exceptional. Pulmonary artery enlargement is present in patients with pulmonary hypertension.

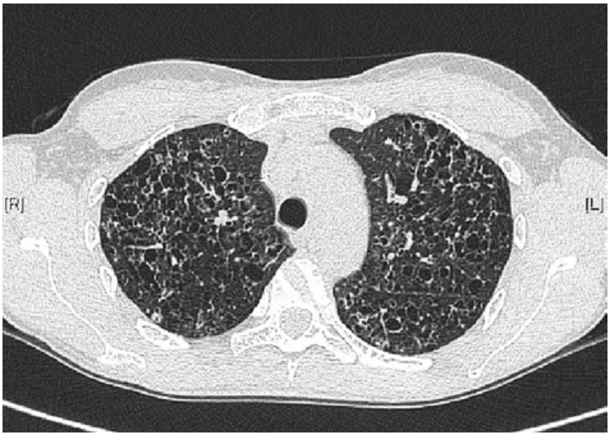


Figure 1. HRCT of the chest demonstrating numerous thin-walled cysts in a patient with pulmonary LCH.

Lung function tests

Lung function may be normal or only mildly impaired in patients with nodular involvement. However, T_{LCO} is usually decreased, including in patients with relatively few lesions on imaging, and air trapping is frequently associated with increased residual volume/TLC ratio. About one third of patients develop airflow obstruction with hyperinflation, which may progress to severe obstructive respiratory insufficiency.

Diagnosis

The gold standard for diagnosing LCH is lung biopsy, which is often obtained during pleurodesis for recurrent pneumothorax. The yield of transbronchial lung biopsy is usually low and experience with transbronchial cryobiopsy is still limited. Bronchoalveolar lavage may support the diagnosis by showing increased number of CD1a$^+$ cells, but with low sensitivity and specificity.

In the appropriate clinical context (young adult smoker), a presumptive diagnosis of pulmonary LCH may be made without biopsy in patients with characteristic HRCT features not requiring drug therapy. Lung biopsy is considered in patients with significant symptoms and impaired or deteriorating lung function, especially if a treatment is contemplated; however, individual evaluation of benefits and risks is warranted. In patients with diffuse cystic lesions on HRCT and severe airflow impairment, lung biopsy may be risky with limited benefit, especially as it may not show characteristic granulomatous lesions at this stage.

Clinical search for extrapulmonary manifestations is warranted. Positron emission tomography–CT may contribute to disease staging at diagnosis.

Evolution

About half of the patients improve following smoking cessation, whereas a large proportion of patients experience a chronic course, with a longitudinal lung function decline of unpredictable severity. Clinical and functional follow-up is therefore warranted for ≥5 years after the diagnosis. A poor outcome with chronic obstructive respiratory failure may occur especially in patients with airflow obstruction and/or hyperinflation at diagnosis. Pulmonary hypertension, often severe, frequently develops in advanced lung disease, after a mean delay of 10 years after diagnosis. Incidence of Hodgkin lymphoma is increased. COPD, and lung cancer and other tumours may develop as a consequence of smoking.

Management of pulmonary LCH

Smoking cessation is absolutely key and is the only measure needed in the majority of patients with pulmonary LCH. Smoking cessation maintained for >6 months is associated with a reduced longitudinal lung function decline and may be followed by improvement of the lung disease.

Management of progressive disease despite prolonged smoking cessation is not standardised and may benefit from a multidisciplinary approach. No randomised controlled trial data are available. Inhaled corticosteroids and bronchodilators are used in subjects with airflow obstruction especially when reactive airway disease is present. Although not based on evidence, oral corticosteroids are often considered in patients with symptomatic and progressive disease with worsening lung function, starting with prednisone 0.5–1 $mg \cdot kg^{-1} \cdot day^{-1}$ then tapered over 6–12 months. Whether improvement, when present, results from treatment efficacy or from spontaneous improvement cannot be established.

Cladribine (2-chloro-deoxyadenosine) has been found to be beneficial in selected cases, with improved lung function and reduced cyst size, occasionally even in patients with advanced disease. Cladribine is under evaluation in a randomised trial (www.clinicaltrials.gov identifier number NCT01473797). However, it may induce profound myelo- and immunosuppression, and should be administered only in expert centres. Vinblastin is generally not effective in adult pulmonary LCH. The use of BRAF inhibitors is promising in patients with systemic LCH but clinical experience is very limited in adult pulmonary LCH; genotype–phenotype correlations and the clinical impact of *MAPK* mutations on treatment indications remain to be further explored.

Long-term supplemental oxygen therapy is prescribed in cases of hypoxaemia. In patients with severe pulmonary hypertension, haemodynamic improvement without worsening gas exchange may be obtained using drugs targeting pulmonary arterial hypertension. Lung transplantation should be considered in patients with end-stage disease but pulmonary LCH may recur in the transplanted lungs, especially if tobacco smoking is resumed.

Further reading

- Emile JF, *et al.* (2016). Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. *Blood*; 127: 2672–2681.
- Grobost V, *et al.* (2014). Effectiveness of cladribine therapy in patients with pulmonary Langerhans cell histiocytosis. *Orphanet J Rare Dis*; 9:191.
- Le Pavec J, *et al.* (2012). Pulmonary Langerhans cell histiocytosis associated pulmonary hypertension: clinical characteristics and impact of pulmonary arterial hypertension therapies. *Chest*; 142: 1150–1157.
- Roden AC, *et al.* (2014). BRAF V600E expression in Langerhans cell histiocytosis: clinical and immunohistochemical study on 25 pulmonary and 54 extrapulmonary cases. *Am J Surg Pathol*; 38: 548–551.
- Tazi A, *et al.* (2015). The natural history of adult pulmonary Langerhans cell histiocytosis: a prospective multicentre study. *Orphanet J Rare Dis*; 10: 30.
- Vassallo R, *et al.* (2017). Current understanding and management of pulmonary Langerhans cell histiocytosis. *Thorax*; 72: 937–945.

Lymphangioleiomyomatosis

Vincent Cottin, Romain Lazor, Claudia Valenzuela and Paolo Spagnolo

Epidemiology and genetics

Lymphangioleiomyomatosis (LAM) is a rare (so-called orphan) lung disease affecting about 3.4–7.8 per million adult women (usually of childbearing age). It may be sporadic or associated with tuberous sclerosis complex (TSC), where it affects 30–40% of adult women and, exceptionally, men. It is recommended that women with TSC aged 18–30 years undergo radiological testing for lung cysts and be followed with serial pulmonary function tests if LAM is present.

TSC is associated with inherited mutations of the *TSC1* and *TSC2* genes. Sporadic LAM is associated with loss of heterozygosity in the *TSC1* or, more frequently, *TSC2* gene. Consequently, the kinase mammalian target of rapamycin (mTOR) signalling pathway is constitutively activated in LAM cells.

Lung pathology

In LAM, the lung parenchyma is progressively replaced by cysts associated with a proliferation of abnormal smooth muscle-like cells and perivascular epithelioid cells (LAM cells). LAM cell proliferation usually develops around lymphatic vessels in the lung and, possibly the axial lymphatics and the thoracic duct. LAM cells are stained with antibodies against smooth muscle actin, desmin and HMB-45 (detecting characteristic pre-melanocyte proteins). As LAM cells have been shown to invade the

Key points

- Lymphangioleiomyomatosis (LAM) is a rare disease of women of childbearing age, characterised by dyspnoea on exertion, relapsing pneumothorax, and multiple thin-walled, round, well-defined, air-filled cysts on chest imaging.
- The diagnosis of LAM can be made if characteristic multiple cysts are present on chest HRCT and associated with tuberous sclerosis, angiomyolipoma, elevated serum vascular endothelial growth factor D level, chylous effusion and/or histopathological confirmation.
- The mammalian target of rapamycin inhibitor sirolimus is approved for the treatment of LAM with abnormal lung function (defined by FEV_1 <70% of predicted) or rapid decline in lung function.
- Sirolimus stabilises lung function in patients with LAM.
- Patients with LAM should be offered ipsilateral pleurodesis after their initial pneumothorax.

lymphatic vessels and spread to selected distant sites such as the lung and kidney, LAM is considered as a low-grade, destructive, metastatic tumor of perivascular epithelioid cells (PEComa).

Circulating LAM cells have been isolated from blood, urine and chylous effusion. The source and physiological counterpart of LAM cells are currently unknown. LAM cell clusters that may derive from lymphatic vessels have been found in the uterus of 90% patients with LAM, suggesting that these cells might originate from this organ. Production by LAM cells of metalloproteases and lymphangiogenic factors such as vascular endothelial growth factor (VEGF)-D may contribute to pathogenesis.

Clinical manifestations and lung function tests

Dyspnea on exertion is the most common symptom. Pneumothorax is the most common mode of presentation and occurs in more than half of the patients during disease course; relapses are very frequent despite pleurodesis. Chylothorax, chylous ascites and lymphangioleiomyomas are frequently seen.

Lung function tests are characterised by airflow obstruction and impaired gas transfer with a decrease in T_{LCO}. Exercise performance and maximal oxygen uptake are impaired. Hypoxaemia is present in advanced disease.

Imaging

Chest radiography shows reticular opacities, cysts, pleural effusion or pneumothorax.

HRCT of the chest plays a major role in diagnosis. It shows characteristic multiple round, thin-walled cysts distributed evenly throughout the lung parenchyma; these cysts may progressively become confluent. Pleural effusion and pneumothorax may also be present.

In TSC, cysts may be associated with small nodules corresponding to multifocal micronodular pneumocyte hyperplasia. The axial lymphatics of the thorax and retroperitoneum may be dilated with lymphadenopathy and retroperitoneal or abdominal lymphangioleiomyomas (in up to 20% of patients) that may result in abdominal discomfort or, rarely, compression.

Angiomyolipoma

Angiomyolipomas (AMLs) of the kidney are benign tumours composed of blood vessels, smooth muscle and adipose tissue easily identified on HRCT. AMLs are found in ~50% of patients with sporadic LAM and 80% of patients with TSC, in whom they are more often bilateral and larger. AMLs may slowly enlarge with time and become prone to bleeding especially when >4 cm in diameter or rich in vascular microaneurysms (percutaneous embolisation or mTOR inhibitors are indicated is such situations). Regular screening for AML is recommended in patients with LAM.

Diagnosis

The differential diagnosis comprises other multiple cystic lung diseases associated with mutations of the folliculin (*FLCN*) gene, especially the Birt–Hogg–Dubé syndrome, and familial isolated primary spontaneous pneumothorax, pulmonary Langerhans' cell histiocytosis, follicular bronchiolitis, cysts associated with lymphoid interstitial pneumonia, nonamyloid immunoglobulin deposition disease, *etc.* A diagnostic work-up searching for alternative causes of multiple cystic lung disease is mandatory, especially if imaging features are not typical for LAM.

The diagnostic gold standard for LAM is lung biopsy showing the pathological features of the disease; however, it is now infrequently performed. Indeed, the combination of characteristic HRCT features with AML or other features of LAM (chylous pleural effusions or ascites and cystic lymphangioleiomyomas) are sufficient to confirm the diagnosis in the absence of biopsy (table 1).

The level of VEGF-D, a major angiogenic growth factor produced by tumour cells, and promoting formation of lymphatic vessels and spread of tumour cells to lymph nodes, is increased in the serum of ~70% of patients with LAM as compared to other cystic lung diseases and healthy controls. Serum VEGF-D level contributes to the noninvasive diagnosis of LAM if elevated (high positive predictive value if >800 $pg \cdot mL^{-1}$) but does not rule out the disease if normal.

When a definite diagnosis is required in patients who have parenchymal cysts on HRCT that are characteristic of LAM, the clinical context is inconclusive and VEGF-D is unavailable or uninformative, biopsy is appropriate; in such cases, transbronchial lung biopsies may be considered before a surgical lung biopsy.

Evolution and prognosis

Disease progression is variable, with some patients remaining relatively stable for long time whereas others deteriorate rapidly with ensuing airflow obstruction and chronic respiratory insufficiency. Median annual FEV_1 decline is ~90 $mL \cdot year^{-1}$ regardless of baseline lung function, yet with large interindividual variability. FEV_1 decline is more rapid in those with greater cyst profusion on CT scanning and in premenopausal subjects compared with postmenopausal subjects. Repeated measurement of FEV_1 and T_{LCO} is used to assess disease progression, with arterial oxygen measurement in advanced disease. Pulmonary hypertension (usually mild) may develop. The median transplant-free survival in patients with LAM is >20 years.

Pharmacological therapy

International guidelines recommend against the use of hormonal therapy, especially progestatives. Oestrogens (contraceptive pill or hormone replacement) may worsen disease progression and should be avoided.

Table 1 Diagnostic criteria for pulmonary LAM

Characteristic lung HRCT (multiple thin-walled, round, well-defined, air-filled cysts) And any of the following:
Presence of TSC
Renal angiomyolipoma (diagnosed by characteristic CT features and/or on pathological examination)
Elevated serum VEGF-D, >800 $pg \cdot mL^{-1}$
Chylous effusion (pleural or ascites) confirmed by tap and biochemical analysis of the fluid
Lymphangioleiomyoma (lymphangioma)
Demonstration of LAM cells or LAM cell clusters on cytological examination of effusion of lymph nodes
Histopathological confirmation of LAM by lung biopsy, or biopsy of retroperitoneal or pelvic masses

The mTOR inhibitor and immunosuppressive agent sirolimus stabilises lung function in patients with LAM. However, side-effects frequently occur, including mouth ulcers, diarrhoea, nausea, increased blood cholesterol levels, skin rash, swelling of the extremities and ovarian cyst formation. Disease progression resumes when sirolimus is stopped. Similar effects are observed with everolimus. mTOR inhibitors are also effective on chylous effusion, lymphangioleiomyomas and in AML not amenable to embolisation therapy. Sirolimus is approved in Europe for LAM. To treat patients with sporadic LAM, the dose of sirolimus is 2 mg daily, with adjustment after 10–20 days to the serum level (target level of 5–15 $ng \cdot mL^{-1}$ or, often, 5–10 $ng \cdot mL^{-1}$). Everolimus is approved in adults with TSC and AMLs at risk of complications but who do not require immediate percutaneous embolisation, or with subependymal giant cell astrocytomas. In LAM, treatment with sirolimus is recommended in patients with abnormal lung function (defined by FEV_1 <70% of predicted) or with rapid decline in lung function.

Inhaled bronchodilators should be prescribed to patients with airflow obstruction and continued if a response is observed. Inhibitors of autophagy and blockers of VEGF or VEGF receptors are being tested.

Management other than drug therapy

Patients with LAM should be offered ipsilateral pleurodesis after their initial pneumothorax rather than waiting for a recurrent pneumothorax before intervening with a pleural symphysis procedure. A previous unilateral or bilateral pleural procedure (*i.e.* pleurodesis or pleurectomy) is not a contraindication to lung transplantation in patients with LAM. Recurrence of LAM on transplant is possible but does not affect survival.

There is a greater risk of pneumothorax and chylous effusion during pregnancy. To become pregnant is the patients' decision; however, pregnancy may be discouraged in patients with severe disease. Influenza and pneumococcus vaccination should be offered to patients with LAM.

Further reading

- Goldberg HJ, *et al.* (2015). Everolimus for the treatment of lymphangioleiomyomatosis: a phase II study. *Eur Respir J*; 46: 783–794.
- Gupta N, *et al.* (2017). Lymphangioleiomyomatosis diagnosis and management: high-resolution chest computed tomography, transbronchial lung biopsy, and pleural disease management. An Official American thoracic Society/Japanese Respiratory Society clinical practice guideline. *Am J Respir Crit Care Med*; 196: 1337–1348.
- Gupta N, *et al.* (2019). The NHLBI LAM Registry: prognostic physiologic and radiologic biomarkers emerge from a 15-Year prospective longitudinal analysis. *Chest*; 155: 288–296.
- Harari S, *et al.* (2018). Recent advances in the pathobiology and clinical management of lymphangioleiomyomatosis. *Curr Opin Pulm Med*; 24: 469–476.
- Johnson SR, *et al.* (2010). European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. *Eur Respir J*; 35: 14–26.
- McCormack FX, *et al.* (2016). Official American Thoracic Society/Japanese Respiratory Society clinical practice guidelines: lymphangioleiomyomatosis diagnosis and management. *Am J Respir Crit Care Med*; 194: 748–761.
- McCormack FX, *et al.* (2011). Efficacy and safety of sirolimus in lymphangioleiomyomatosis. *N Engl J Med*; 364: 1595–1606.

Pulmonary alveolar proteinosis

Paolo Palange and Francesco Vaccaro

Pulmonary alveolar proteinosis (PAP) is a rare syndrome occurring worldwide with an estimated prevalence of 0.2–0.6 cases per 100 000 individuals. PAP is characterised by accumulation of surfactant within alveolar macrophages in the alveoli and terminal airspaces, with impairment of gas transfer, and by a variable clinical course, ranging from spontaneous resolution to progressive respiratory failure.

Surfactant clearance impairment is the likely common pathophysiology of PAP, which can be classified as follows.

- Auto-immune PAP (90–95%) is most common in adults and is due to disruption of granulocyte–macrophage colony-stimulating factor (GM-CSF) signalling by the presence in the plasma and lungs of high levels of neutralising anti-GM-CSF autoantibodies (GMAb). Passive transfer of PAP features in monkeys inoculated with human GMAb strongly support the concept that GMAb are the causative factor of autoimmune PAP.
- Secondary PAP (5–10% of adult cases) occurs as a consequence of the presence of several underlying diseases associated with PAP, such as haematological disorders (mostly myelodysplastic syndrome), immunodeficiency, infections (*e.g.* HIV, cytomegalovirus and *Pneumocystis jirovecii*), drugs (*e.g.* antineoplastics and immunosoppressors), dust inhalation or lysinuric protein intolerance.
- Congenital or hereditary PAP (<1%) is characterised by surfactant production disorders due to mutations in the genes encoding surfactant protein (SP)-B and SP-C, ABCA3 (ATP-binding cassette subfamily), and TTF-1 (thyroid transcription factor 1). In addition, genetic defects in GM-CSF α or β may be involved.

Key points

- Pulmonary alveolar proteinosis (PAP) is a rare syndrome caused by impairment of surfactant clearance.
- 90% of PAP cases are associated with the presence of neutralising granulocyte–macrophage colony-stimulating factor (GM-CSF) autoantibodies (GMAb) (autoimmune PAP).
- Diagnosis of primary autoimmune PAP is based on the triad of: 1) ‘crazy paving’ pattern on HRCT; 2) milky appearance and cytology of bronchoalveolar lavage fluid; and (3) elevated serum level of GMAb.
- Whole-lung lavage is the current standard of care for PAP but alternative therapies (especially GM-CSF administration) are under active investigation.

- Unclassified PAP (<1%) is defined when the patient is negative for GMAb and there are no secondary or congenital/hereditary causes present.

According to a recently published meta-analysis and large cohort report, 90% of immune PAP patients are middle-aged adults complaining of progressive exertional dyspnoea and cough; interestingly, about one-third of a large Japanese PAP series was asymptomatic. Physical examination of PAP patients is often unremarkable. Pulmonary function tests may be normal but, usually, the first abnormality is represented by a decrease in lung diffusing capacity and increased exertional alveolar–arterial oxygen tension gradient. The classic chest radiographic presentation is a diffuse bilateral infiltrate with a distribution that is sometimes similar to that of pulmonary oedema (figure 1a). More typical is the HRCT presentation defined as 'crazy paving' (thickening of interlobular and intralobular septa, and ground-glass opacities, with a patchy distribution) (figure 1b), which is very often associated to autoimmune PAP (83%) but unusual in the secondary forms. Although biopsy, usually transbronchial, is considered mandatory to establish the correct diagnosis of PAP, more recently, the triad represented by

1) typical crazy paving pattern on HRCT,

2) macroscopic appearance of milky fluid and cytology of bronchoalveolar lavage fluid, and

3) elevated serum level of GMAb

is now considered sufficient to establish the diagnosis of autoimmune PAP (sensitivity and specificity 100%). Lung biopsy should be considered when one or more of the previous findings is unclear. Histopathology usually shows well preserved alveolar wall architecture, and alveolar spaces filled with lipoproteinaceous, eosinophilic, periodic acid–Schiff-positive material, and foamy macrophages.

The natural history of the PAP has been greatly influenced by the treatment. Before whole-lung lavage (WLL) came into use, progressive deterioration occurred in 30% of PAP patients. Death occurred mostly because of irreversible respiratory failure and, to a lesser extent, respiratory infection. The latter is a typical complication of the clinical course of PAP: pulmonary and systemic infections due to opportunistic organisms such as *Nocardia*, mycobacteria and *Cryptococcus* are often reported. Increased susceptibility to lung infections is traditionally attributed to the impairment of alveolar macrophages engulfed by surfactant but systemic infections have been ascribed more recently to GM-CSF signalling impairment (inducing a defect in phagocytosis).

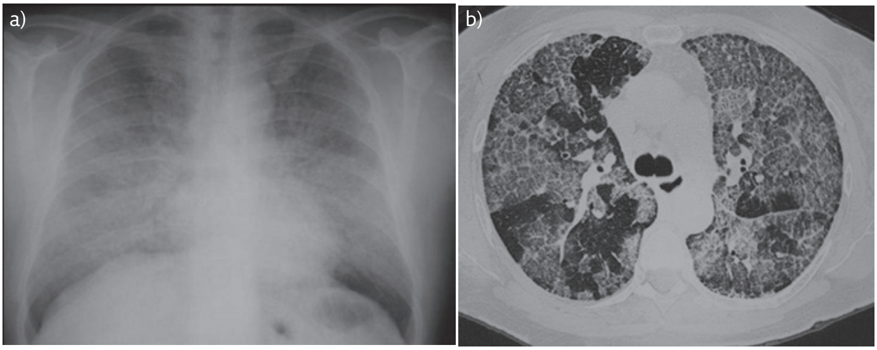


Figure 1. a) Radiographic and b) HRCT 'crazy paving' presentation of PAP.

The adoption of WLL, first described in the mid-1960s, has changed the natural history of PAP by dramatically reducing the death rate. It is considered the standard of care for PAP and 95% of PAP patients respond positively to the procedure, although a considerable fraction of patients may show relapses or incomplete resolution.

Corticosteroids are not indicated in autoimmune PAP; they should be used only for those patients with concomitant connective tissue disease or other steroid-responsive processes (e.g. haematological diseases).

GM-CSF administration, based on the pathophysiology of the disorder, is considered an attractive alternative to WLL. Unfortunately, limited experience and, more importantly, poor access to the drug have so far precluded diffusion of this therapeutic option. Possible alternatives are plasmapheresis or immunosuppressive agents such as rituximab, but data are so far insufficient. Lung transplantation is considered in end-stage disease but PAP may recur.

Further reading

- Bonella F, *et al.* (2012). Wash-out kinetics and efficacy of a modified lavage technique for alveolar proteinosis. *Eur Respir J*; 40: 1468–1474.
- Campo I, *et al.* (2016). Whole lung therapy for pulmonary alveolar proteinosis: a global survey of current practice and procedures. *Orphanet J Rare Dis*; 11: 115.
- Inoue Y, *et al.* (2008). Characteristics of a large cohort of patients with auto-immune pulmonary alveolar proteinosis in Japan. *Am J Respir Crit Care Med*; 177: 752–762.
- Kumar A, *et al.* (2018). Pulmonary alveolar proteinosis in adults: pathophysiology and clinical approach. *Lancet Respir Med*; 6: 554–565.
- Luisetti M, *et al.* (2010). Pulmonary alveolar proteinosis. In: Schwarz MI *et al.*, eds. *Interstitial Lung Disease*, 5th Edn. Maidenhead, McGraw-Hill.
- Orphanet (2009). Activity Report. www.orpha.net/orphacom/cahiers/docs/GB/Activity Report2009.pdf
- Ramirez J, *et al.* (1963). Pulmonary alveolar proteinosis: a new technique and rationale for treatment. *Arch Int Med*; 112: 419–431.
- Sakagami T, *et al.* (2009). Human GM-CSF autoantibodies and reproduction of pulmonary alveolar proteinosis. *N Engl J Med*; 361: 2679–2681.
- Seymour JF, *et al.* (2002). Pulmonary alveolar proteinosis: progress in the first 44 years. *Am J Respir Crit Care Med*; 166: 215–235.
- Suzuki T, *et al.* (2010). Hereditary pulmonary alveolar proteinosis: pathogenesis, presentation, diagnosis, and therapy. *Am J Respir Crit Care Med*; 182: 1292–1304.
- Trapnell BC, *et al.* (2003). Pulmonary alveolar proteinosis. *N Engl J Med*; 349: 2527–2539.
- Uchida K, *et al.* (2007). GM-CSF auto-antibodies and neutrophil dysfunction in pulmonary alveolar proteinosis. *N Engl J Med*; 356: 567–579.

Amyloidosis

Helen J. Lachmann

Amyloidosis is a group of diseases caused by accumulation of fibrillary deposits in the extracellular space. These progressively disrupt the structure and function of affected tissues. Diagnosis is histological, by Congo red staining, and classification is according to the fibril precursor protein. It may be either acquired or inherited, and at least 30 different proteins can form amyloid fibrils in humans. Untreated, systemic amyloidosis progresses relentlessly, but it can regress if the supply of fibril precursors is reduced.

Amyloidosis can present to respiratory physicians in a number of ways:

- chronic lung conditions can give rise to systemic amyloidosis;
- systemic amyloidosis may present with respiratory symptoms; and
- localised pulmonary and respiratory tract amyloid deposits may present symptomatically or incidentally.

Systemic amyloidosis complicating respiratory diseases

Amyloid A amyloidosis

This causes proteinuric renal failure and is a potential complication of any sustained inflammatory condition. The amyloid fibrils are derived from the acute phase reactant, serum amyloid A protein (SAA). The major respiratory disease underlying amyloid A (AA) amyloidosis in the industrialised world is bronchiectasis. Previously, TB was common and other respiratory associations include CF, sarcoidosis, lung neoplasia and Kartagener syndrome. The prognosis of AA amyloidosis depends on the degree of renal damage and whether the underlying inflammatory disease can be completely controlled. Treatment is targeted at the underlying disease and may involve surgery, antimicrobials or immunosuppression.

Key points

- Amyloidosis is a protein deposition disease.
- Diagnosis is by biopsy and Congo red staining.
- Systemic amyloidosis is a life-threatening condition that usually affects several organs.
- Localised amyloidosis can present with obstructive symptoms, haemoptysis or as an incidental finding on imaging.
- Treatment depends on the type and distribution of amyloid deposits.

Amyloid light chain amyloidosis

This may complicate any B-cell dyscrasia as the fibrils are derived from monoclonal immunoglobulin light chains. A number of chest conditions can underlie systemic amyloid light chain (AL) amyloidosis including Sjögren syndrome, plasmacytomas and Castleman tumours.

Respiratory system symptoms arising from systemic AL amyloidosis

Although lung deposits are universal on *post mortem*, symptoms are rare and dyspnoea generally reflects amyloid cardiomyopathy. Chest radiographs are usually normal. Lung function tests may be restrictive and extensive alveolar deposits can reduce gas transfer. Persistent pleural effusions are usually due to cardiac infiltration by amyloid but can rarely be caused by amyloidotic disruption of the pleura and may require recurrent drainage or pleurodesis. Sleep disordered breathing is recognised, presumably reflecting cardiomyopathy, macroglossia, neuropathy and myopathy.

Treatment of systemic AL amyloidosis is chemotherapy directed against the underlying B-cell clone. Some agents, such as proteasome inhibitors and immunomodulatory imide drugs, are reported, albeit rarely, to cause lung toxicity.

Amyloidosis localised to the respiratory tract

This results either from local production of fibril precursors or from a microenvironment that favours fibril formation from a widely distributed protein. The majority of deposits are AL type associated with low grade B-cell clones confined to the affected site. Apparently localised amyloid deposits can be manifestations of systemic disease and should always be fully investigated to exclude systemic amyloidosis.

Laryngeal amyloidosis

Amyloid represents 0.5–1% of benign laryngeal disease and the incidence increases with age. It usually presents as hoarseness and is relatively benign but can be progressive or recur after treatment. Fatal haemorrhage has been reported. Endoscopic or laser excision is the treatment of choice, aiming to preserve voice quality and airway patency. External beam radiotherapy has been used in recurrent AL type disease. Very rarely apparently localised laryngeal amyloid deposits can be a feature of hereditary apolipoprotein AL amyloidosis.

Tracheobronchial amyloidosis

This typically presents in the fifth or sixth decades with dyspnoea, cough and haemoptysis. Airway narrowing may cause pneumonia or lobar collapse and solitary nodules can mimic endobronchial neoplasia. MRI is useful in diagnosis and evaluating disease extent. There is no proven therapy although chemotherapy has been tried in patients with progressive disease. Management is dictated by symptoms and includes resection, stenting, laser ablation or external beam radiotherapy. The prognosis is guarded with 45% survival at 6 years.

Parenchymal pulmonary amyloidosis

This is typically an incidental finding on chest radiography. Amyloid nodules are usually peripheral and subpleural in the lower lobes; they may be bilateral and range from 0.4–15 cm. Growth is slow and nodules may cavitate or calcify. Histology is often required for differentiation from neoplasia and prognosis is usually excellent without specific treatment. There is a recognised association with Sjögren syndrome.

Mediastinal and hilar amyloid lymphadenopathy

The lymphadenopathy may be massive and typically complicates a low-grade lymphoma. Disease progression is slow and calcification frequent. Tracheal compression or superior vena cava obstruction occasionally result.

Conclusion

Amyloidosis can both complicate longstanding pulmonary diseases and be deposited within the respiratory system. The presentation and prognosis of amyloid deposits depend on their aetiology and distribution and can be benign or life threatening. In most cases of localised disease, management is essentially supportive or involves resection of symptomatic deposits. In contrast, systemic treatment can be extremely effective in patients with generalised AA and AL amyloidosis.

Further reading

- Iadanza MG, *et al.* (2018). A new era for understanding amyloid structures and disease. *Nat Rev Mol Cell Biol*; 12: 755–773.
- Khoor A, *et al.* (2017). Amyloidosis of the lung. *Arch Pathol Lab Med*; 2: 247–254.
- Mahmood S, *et al.* (2015). Natural history and outcomes in localised immunoglobulin light-chain amyloidosis: a long-term observational study. *Lancet Haematol*; 2: e241–e250.
- Milani P, *et al.* (2017). The lung and amyloidosis. *Eur Respir Rev*; 26: 170046.
- Phillips NM, *et al.* (2017). Laryngeal amyloidosis: diagnosis, pathophysiology and management. *J Laryngol Otol*; 131: S41–S47.
- Parambil JG, *et al.* (2006). Interstitial lung disease in primary Sjögren syndrome. *Chest*; 130: 1489–1495.

Drug-induced and iatrogenic respiratory disease

Philippe Camus and Philippe Bonniaud

Key points

- Drug-induced respiratory disease (DIRD) is a common diagnostic consideration in pulmonology, oncology, internal medicine, intensive care and family practice.
- The lung parenchyma, tongue, mouth floor, larynx, trachea, small airways, pleurae, pulmonary circulation, neuromuscular system and Hb can all be involved.
- Drug-induced cardiotoxicity deserves consideration as this can lead to chest pain, myocardial ischaemia, myocarditis, heart block, HF and acute pulmonary oedema.
- Acute interstitial lung disease and upper airway angio-oedema can be immediately life threatening, requiring immediate management.
- Amiodarone, immune checkpoint inhibitors, chemotherapy agents, methotrexate, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, salicylate, hydrochlorothiazide and β-blockers (among 1500 possible offending drugs, chemicals and procedures) pose particular risks of, sometimes severe, adverse respiratory effects.
- The clinical, imaging and pathological expression of DIRD may mimic illnesses of other causes or that occur idiopathically. However, it is unusual for pathology to be specific for drug aetiology.
- Diagnosing DIRD requires a high degree of awareness, up-to-date information (www.pneumotox.com), and ruling out of other causes and conditions, particularly infection, using alveolar lavage and appropriate tests.
- Stopping the drug may be followed by improvement in signs, symptoms, lung physiology, gas exchange and imaging.
- Corticosteroid therapy is preferred for cases with severe presentation and where de-challenge does not translate into some improvement. Duration of corticosteroid therapy varies with drug, pattern and response.
- Extreme care must be taken to avoid re-exposure to the drug, which may lead to severe relapse of the adverse reaction. Thus, re-challenging the patient for diagnostic purposes is not recommended.

The scope of drug-induced lung disease (DILD)/drug-induced respiratory disease (DIRD) has expanded from 120 drugs in the 1970s to >1500 drugs, agents, substances, chemicals and procedures. Drugs cited by the 1980s (*e.g.* amiodarone, hydrochlorothiazide, methotrexate, nitrofurantoin and salicylate) are still prevlant. Recent entries include inhibitors of the tyrosine kinases and tumor necrosis factor-α, and immune checkpoint inhibitor (ICIs). ICIs cause an array of immune-related adverse reactions in various organs, including lung. DIRD is a diagnosis of exclusion, in that all other aetiologies must be carefully ruled out. Possible clinical, imaging, HRCT, bronchoalveolar lavage (BAL) and pathological patterns of iatrogenic involvement have also increase to >700. DIRD is a common consideration in oncology, cardiology, rheumatology, internal and emergency medicine, intensive care, and pulmonary and family practice. DIRD may progress rapidly and become life threatening within minutes, requiring emergent diagnosis, cessation of exposure to the drug, and appropriate management. Serious drug-induced/iatrogenic adverse reactions include drug-induced angio-oedema and consequent acute suffocation, acute respiratory failure from pulmonary oedema, acute interstitial lung disease (ILD), eosinophilic pneumonia, organising pneumonia, alveolar haemorrhage and/or acute respiratory distress syndrome (ARDS), alongside catastrophic bronchospasm, pneumothorax, foreign body pulmonary embolism, neuromuscular paralysis, coma, anaphylaxis and methaemoglobinaemia. Overall, 15% of all iatrogenic respiratory reactions are life threatening and 2.5–9% can be fatal and a proportion of deaths is avoidable *via* improved knowledge, repeated drills, implementation of existing guidelines, early diagnosis, drug withdrawal and appropriate treatment including ventilatory support, corticosteroids, and specific antidotes to reverse toxicity from opioids, methaemoglobinaemia-inducing drugs or anticoagulants.

Iatrogenic, as opposed to drug-induced, respiratory injury encompasses adverse effects from therapy drugs, haemotherapy, radiation therapy, contrast media, medical (*e.g.* cryoablation for atrial fibrillation) and surgical procedures (*e.g.* pleural effusion or effusions following coronary artery bypass grafting), acupuncture, and infections resulting from immunosuppressive drugs including corticosteroids. Beyond drugs, history taking and diagnostic workup in patients suspect of having drug-induced respiratory injury include exposure to e-cigarette vapour/mist, illicit street drugs, abused natural or synthetic substances including those available on the Internet, dietary herbal or mineral compounds, adulterants, excipients and vehicles including paraffin and fillers, rodenticides, toxic chemicals, household compounds, terror/warfare agents and targeted weapons. Adult patients, children, bystanders and law enforcement personnel can be indirect victims of drugs, illicit substances and chemicals. A few drug reactions in children or in the aged occur by proxy. An updated list of potentially harmful drugs, agents, substances, chemicals and procedures is available at https://www.pneumotox.com.

General features of DIRD

Drugs may injure the lung regardless of the route of administration (be it oral, intravenous, intramuscular (the three most common), topical (*e.g.* eye drops or dermal) or intracavitary (pleural space, urinary bladder, intrathecal or gynecological system)). Usually, drugs directly injure the lung parenchyma, central, large or small airways, pulmonary circulation, pleural membrane, lymph nodes, mediastinum, lymphatics, respiratory muscles, neuromuscular system or Hb, causing corresponding patterns of dysfunction. Less often, drugs initiate and mimic a systemic illness (*e.g.* anaphylaxis, drug rash with eosinophilia and systemic syndrome (DRESS), lupus with antinuclear antibodies, vasculitis with or without anti-proteinase

(PR)3 and/or anti-myeloperoxidase (MPO) anti-neutrophil cytoplasmic antibodies (ANCAs), eosinophilic granulomatosis and polyangiitis, sarcoid-like granulomatosis, myasthenia gravis, or other immune-related adverse reactions) that may damage the lung in isolation and/or other organs concomitantly. Drug withdrawal is a mainstay of diagnosis when this translates into reversal of the reaction, saving patients unnecessary investigation, corticosteroid therapy and immunosuppressive drugs.

Because of the proximity and physiological interactions of lungs and heart, iatrogenic cardiac injury also deserves consideration. Cardiotoxicity is an increasingly recognised complication of anticancer therapies including anthracyclines, trastuzumab and ICIs. Cardiotoxicity is in the form of chest pain, myocarditis, myocardial ischaemia, infarction or dysfunction, HF, pulmonary oedema, dysrhythmias, heart block, pleural effusion and/or pericardial tamponade. It is essential to rapidly identify and withdraw the culprit drug or drugs, taking into account the required therapy for the underlying disease, which may exhibit a flare if the drug or drugs are withdrawn abruptly. It is essential to manage drug-induced airway compromise using endoscopy, intubation or tracheostomy; respiratory failure using oxygen therapy, corticosteroid therapy, mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO); pleural/pericardial effusion or pneumothorax by removal of fluid or exsufflation; and cardiovascular instability with appropriate drug and mechanical support.

Common offenders causing iatrogenic respiratory disease

Common iatrogenic agents causing respiratory disease include amiodarone; nitrofurantoin; salicylate; hydrochlorothiazide; anticoagulants; methotrexate; chemotherapy drugs (nitrosoureas, cyclophosphamide, busulfan and oxaliplatin); nucleoside analogues; ibrutinib; small biological molecules inhibiting tyrosine kinases (imatinib, dasatinib, nilotinib, erlotinib, gefitinib, crizotinib and osimertinib); antagonists of tumour necrosis factor (TNF)-α (adalimumab, infliximab and etanercept); other disease-modifying anti-rheumatic drugs; inflammatory bowel-disease modifying drugs; ICIs targeting the cytotoxic T-lymphocyte antigen 4, programmed death (PD)-1 or PD-1 ligand 1/2 pathway (atezolizumab, avelumab, durvalumab, ipilimumab, nivolumab, pembrolizumab and tremelimumab); monoclonal antibodies used to treat neoplastic conditions (bevacizumab and cetuximab); and oral novel anticoagulants (*e.g.* abciximab, apixaban and rivaroxaban). Drug regimens used to treat viral hepatitis C or HIV infection may also cause diffuse lung injury. Cryoablation for neutralisation of atrial fibrillation circuits has been linked to a constellation of potentially life-threatening adverse effects involving the pulmonary vein, heart, phrenic nerve or oesophagus.

Pathophysiology: mechanisms of injury

No unifying mechanism can explain all DIRD. Drugs may cause mechanism-based on-target adverse reactions (*e.g.* bleeding from anticoagulants or antiplatelet agents, or infections from corticosteroid therapy, immunosuppressive drugs or TNF-α antagonists). Drugs in certain pharmacological classes can produce a stereotyped pattern of involvement (*e.g.* β-blocker- and nonsteroidal anti-inflammatory drug (NSAID)-induced bronchospasm, NSAID- or antibiotic-induced eosinophilic pneumonia, chemotherapy-related noncardiac pulmonary oedema, diffuse alveolar damage (DAD) and ARDS, ergot-induced pleural pathology, or ICI-related pulmonary, cardiac or other organ injury). Such adverse reactions may be related to the pharmacological effect of the drug family, even though the pharmacophores differ. Caution is needed when using a congener drug of the same class as a substitute, since cross-reactions can occur in some instances (*e.g.* rheumatoid arthritis or cardiac patients who need long-term therapy but who are intolerant to NSAIDs or aspirin, incremental doses of the drug can be given to reach a state of tolerance that can be maintained on continued exposure to the drug, otherwise intolerance may recur).

Drug-induced asthma and bronchospasm (194 causal drugs) is largely a non-IgE-dependent phenomenon. Hypersensitivity reactions (73 drugs) and anaphylaxis (204 drugs) induced by platinum salts (acquired while receiving treatment) or cetuximab (constitutional or acquired before onset of treatment due to cross-reaction with tick antigens) can be IgE mediated.

Angiotensin-converting enzyme (ACE) inhibitor-associated upper airway angio-oedema is likely due to accumulation of bradykinin and substance P, which are normally degraded by ACE. The incidence of this complication is greater in non-white individuals.

Pharmacokinetics and metabolism in lung tissues can be relevant for a few drugs and chemicals. Amiodarone and its main metabolite desethylamiodarone concentrate in lysosomes in several lung cell types, including pneumocytes, endothelial cells, histiocytes and macrophages, disturbing phospholipid catabolism in those cells, as exemplified by foamy macrophages in BAL fluid and tissues of amiodarone toxicity patients. Elevated dosages of amiodarone are associated with an increased likelihood of toxicity. Slow and limited efflux of amiodarone and its metabolites likely explains the slow spontaneous resolution of amiodarone pulmonary toxicity (APT) following isolated drug discontinuance and why the disease may relapse after amiodarone withdrawal at a time when corticosteroid therapy given to treat APT is being tapered. Alkylating agents (nitrosoureas, cyclophosphamide and bleomycin) may exert dose-dependent cytopathic toxicity on type I and II pneumocytes and surfactant dysfunction at the air–tissue interface. Mammalian target of rapamycin (mTOR) inhibitors and radiation therapy demonstrate dose-dependent toxicity; identification of a threshold dose above which toxicity is more likely to occur may help stay maintain a safe dose. Likewise, slow as opposed to rapid *i.v.* infusions of bleomycin and maintenance of adequate renal function are important as regards risk reduction.

Bioactivation of drugs may take place in microsomes of specialised lung cells, in the form of oxidative or reductive metabolism. This may generate reactive metabolites or oxygen species, respectively. Metabolism of bleomycin, cyclophosphamide, mitomycin, nitrofurantoin and paraquat in specific lung cells may produce active intermediates that may cause cell stress, depletion of reducing equivalents, cell damage and death, followed by inflammation and/or fibrosis. The heterogeneous distribution of activating enzymes in lung cells may explain targeted alveolar or bronchiolar toxicity from drugs and naphthalene. In addition to being toxic by themselves, elevated inspired fractions of oxygen may exacerbate lung injury caused by amiodarone, bleomycin, chemotherapy and radiation, by fuelling reactive oxygen production. Attention is required in patients who are being treated with or who were previously exposed to the above drugs as delayed oxygen-triggered acute ‘recall’ toxicity may develop. Prudent oxygenation during anaesthesia is warranted, targeting, for instance, 90% S_{pO_2} instead of liberally administering oxygen.

Immune-related adverse events from ICIs may rest on influx of inflammatory/immune cells in various organs, including the lung. Shared antigens between the tumour and normal tissues may play a role in driving the autoimmune adverse reaction.

In drug addicts, lung injury can result from the deposition of drug and excipients in the distal pulmonary circulation or around small airways, followed by reactive foreign body granulomas and/or fibrosis, causing irreversible obstructive airway dysfunction, and/or pulmonary hypertension.

In most other instances, DIRDs do not seem to be target or mechanism based as they develop unexpectedly in a subset of individuals who may be predisposed because of a distinct genetic trait. The location of the adverse drug reaction within the respiratory system is of importance for the clinical expression of toxicity.

Epidemiology

Interstitial/infiltrative lung disease and its subtypes are the most common expression of DIRD, with about three quarters of all iatrogenic respiratory disease (IRD) presenting in this manner. Drugs account for 3–5% of all ILD. Regarding ILD subgroups, approximately 8–10% of all ARDS, 11% of alveolar haemorrhage, 10–25% of eosinophilic pneumonias and 25–30% of organising pneumonia cases are due to drugs. The greatest incidence is with chemotherapeutic agents (bleomycin (up to 50%, depending upon drug regimen and which tests are used to diagnose the condition), amiodarone (2–4%), methotrexate (0.5–1%), mTOR inhibitors (up to 35%) and nitrofurantoin (0.2%)), antibiotics, TNF-α antagonists, tyrosine kinase inhibitors (TKIs), ICIs (up to 16%) and radiation therapy. Combination of chemotherapeutic agents or chemotherapy and radiation or disease-modifying antirheumatic drugs may increase the likelihood of developing toxicity.

Agents causing patterns other than ILD with significant incidence include ACE inhibitors, aspirin, β-blockers, biologics, cetuximab, corticosteroids, dasatinib, ergolines, fentanyl and its synthetic derivatives, haemotherapy (transfusion of blood or blood components), hydralazine, hydrochlorothiazide, ICIs, infliximab, inhalants, levamisole, neuromuscular blocking agents, NSAIDs, opiates, aspirated pills, propylthiouracil, platinum salts, silicone and paraffin.

The literature on the topic exceeds 35000 references, which have been reviewed before listing in Pneumotox.

Investigations: diagnostic workup

Imaging in IRD

Imaging can be distinctive ILD, pulmonary oedema (cardiogenic or noncardiogenic, the latter with normal-sized heart and/or pulmonary capillary wedge pressure), alveolar haemorrhage, central airway involvement, pleural pathology, certain pulmonary embolic vasculopathies, mediastinal involvement and cardiotoxicity . However, rarely is imaging suggestive of the drug aetiology *per se*. Abnormalities on imaging may be inconspicuous in drug-induced pulmonary hypertension or airway disease. Imaging and pathology correlates are shown in table 2. Using pathological terms to label imaging patterns (so-called histospecific imaging patterns) is a growing issue. Patterns are largely not specific for pathology, even less so for drug-induced pathological patterns. They cannot reliably exclude an infection. Reproducibility has not been tested.

The extent of involvement on imaging tends to correlate with impairment of gas exchange. In general, the expression of DILD is in the form of haze, ground glass or sometimes a miliary pattern, and reticulation of septal thickening. Eosinophilic pneumonias may manifest with opacities having a preferential subpleural and upper distribution. Acute nitrofurantoin lung takes the form of diffuse haze and small pleural effusions, while subacute/chronic nitrofurantoin pulmonary toxicity may exhibit peribronchovascular consolidation or may mimic pulmonary fibrosis with reticulation and diminished lung volumes. Drug-induced organising pneumonia may present with migratory opacities on serial imaging, a mass with air bronchogram, or diffuse involvement and respiratory failure. The pulmonary opacities in exogenous lipoid pneumonia typically exhibit a

Table 1. DIRD management checklist

1) Maintain a high degree of awareness and suspicion for the drug/iatrogenic aetiology in the clinic at all times. Where appropriate, check Pneumotox by drug(s) or pattern(s). Download pertinent literature from Pneumotox if needed.
2) When evaluating severe or life-threatening emergencies presumed to be drug-induced (*e.g.* anaphylaxis, bronchospasm, suffocation, asphyxia, diffuse white-out, ARDS, pulmonary bleeding, pericardial tamponade, respiratory muscle paralysis, methaemoglobinaemia), such emergent management as maintenance of airway patency, oxygen therapy and/or mechanical ventilation should be placed ahead of causality assessment. Remove any nonvital drug.
3) Evaluate complete blood count, electrolytes, renal function, coagulation, autoimmunity including ANA, ANCA, anti-HNE and bacterial/viral panel. Compare with prior values if any.
4) Take a complete drug history including current or past exposure to medications, abused substances, herbals, chemicals, radiation therapy and/or procedures. If patient unable to answer, contact family, relatives, acquaintances or pharmacy.
5) Should identification and/or measurement of drug or drugs in body fluids be indicated, have this sampled as early as possible, since spontaneous drug clearance may prevent proper identification or measurement after a few days off the drug.
6) Retrieve and view any imaging and pulmonary function recorded prior to therapy with the drug.
7) Delineate the pattern of involvement as accurately and as noninvasively as possible, using clinical presentation, pulmonary function, imaging including HRCT and BAL. A lung biopsy is rarely indicated as this stage because of non-specificity.
8) Examine the possible causal role of the underlying disease (*e.g.* connective tissue disease, rheumatoid arthritis, HF, malignancy), an infection or an incidental condition.
9) Correlate timing of exposure to drug(s) *versus* onset of clinical presentation. Depends on both drug and pattern, and may range from minutes for bronchospasm or anaphylaxis to years for ILD.
10) Match each drug and pattern for best coherence using Pneumotox and decide whether drug discontinuation is or was appropriate, underlying condition permitting.
11) Evaluate causality, *e.g.* Naranjo scale.
12) Decide on corticosteroid therapy, depending on response to drug discontinuance, severity, extent, progression of the reaction and expected effect. Improvement may follow within hours, weeks or more, depending on drug, pattern and if an antidote can be given in addition.
13) Organise follow-up for resolution of signs, symptoms, pulmonary physiology and imaging.
14) Consider re-challenge only if drug is vital or with the purpose of inducing tolerance. Make sure the patient will otherwise never be re-exposed to the drug.
15) Comply with local requirement for notification of adverse effects of drugs to regulatory agencies.

HNE: human neutrophil elastase.

Table 2. Main imaging–pathological patterns of DIRDs

Pattern on chest radiograph or HRCT	Causal drugs/agents (Pneumotox sections XVI–XV)	Possible pathological correlate
Diffuse haze	Drugs that cause interstitial pneumonia (NSIP-like)	Interstitial/alveolar inflammation
	Drugs that cause mild pulmonary oedema, DAD or DAH	Moderate oedema, DAD, DAH
Ground-glass opacity, diffuse	Chemotherapy agents	Pulmonary oedema, alveolar haemorrhage, DAD, cellular NSIP
	Drugs causing NSIP	
Ground-glass opacity, localised	Radiation therapy	Early radiation lung injury (interstitial oedema, cell sloughing, cell debris) in the field
	Paraffin	Alveolar filling with mineral oil and lipid-laden macrophages
	Amiodarone	Localised APT
Diffuse white-out	Drugs that produce acute pulmonary oedema, ILD, eosinophilic pneumonia, DAD or DAH[#]	Pulmonary oedema/flooding, alveolar fibrin, cellular interstitial pneumonitis, eosinophilic pneumonia, DAD, DAH
Disseminated ground-glass opacity with a mosaic pattern of distribution	Drugs that cause interstitial pneumonia, including ICIs	Cellular interstitial pneumonia
	Nitrofurantoin	Desquamative interstitial pneumonia
Bilateral perihilar alveolar opacities with a batwing/butterfly pattern of distribution	Drugs that cause pulmonary oedema, DAD or DAH	Pulmonary oedema, DAD, DAH
Subpleural areas of consolidation	Drugs that cause PIE or OP	Eosinophilic pneumonia or OP
Opacities with a recognisable segmental or lobar pattern of distribution	Amiodarone	Localised phospholipidosis or OP
	Statins	OP
	Paraffin	Exogenous lipoid pneumonia

(*Continued*)

Table 2. Continued

Pattern on chest radiograph or HRCT	Causal drugs/agents (Pneumotox sections XVI–XV)	Possible pathological correlate
Miliary pattern	BCG therapy	Granulomatous reaction
	Methotrexate	Granulomatous reaction
	Sirolimus	Granulomatous reaction
	Drugs that cause a granulomatous pulmonary reaction	Granulomatous reaction
Area or areas of consolidation	Drugs that cause OP or eosinophilic pneumonia	PIE/OP
	ICIs	OP
A mass or masses	Amiodarone	Phospholipidosis inflammation/OP
	Amiodarone	Amiodaronoma
	Paraffin	Paraffinoma
Wandering opacities	Drugs that cause OP or PIE (*e.g.* statins, amiodarone)	Mostly OP
		Eosinophilic pneumonia
	Following irradiation for breast carcinoma	OP
Multiple nodular opacities	Amiodarone	APT+sterile central necrosis
	Bleomycin	OP
	Bleomycin	Areas of nodular fibrosis
Pulmonary fibrosis	Chemotherapy drugs	Pulmonary fibrosis
	Amiodarone	Fibrotic NSIP–UIP pattern
Diminished lung volume on chest radiography	Amiodarone	Pulmonary fibrosis?
	Nitrofurantoin	Pulmonary fibrosis?
	Chemotherapy agents	Pulmonary fibrosis?
	Irradiation	Pulmonary fibrosis?
	Drugs causing respiratory paralysis or coma	Atelectasis?

NSIP: nonspecific interstitial pneumonia; OP: organising pneumonia; BCG: bacille Calmette–Guérin; UIP: usual interstitial pneumonia. $^{\#}$: see appropriate pattern at www.pneumotox.com.

predilection for the lower lung zone and show low attenuation; pulmonary arteries can be spontaneously visible within the involved area on unenhanced CT. APT usually takes the form of asymmetric pulmonary opacities with a recognisable segmental or lobar distribution, or in the form of shaggy nodules. Areas of consolidation can be electron dense due to the iodine atoms in the amiodarone molecule. With time, APT can progress to pulmonary fibrosis. Early antineoplastic chemotherapy toxicity is in the form of a faint haze or ground glass corresponding pathologically to pulmonary oedema and/or alveolar damage, while later cases may resemble pulmonary fibrosis.

Radiation pneumonitis develops preferentially along the path of the radiation beam and resulting changes are more in the areas with greatest radiation metrics. Stereotactic body radiation therapy produces a circumscribed round, circumvoluted or whorled area of pneumonitis, with decreasing standardised uptake value numbers with time from radiation therapy. In addition to the main patterns listed in table 2, HRCT may disclose inter- and/or intralobular septal thickening, disseminated lobular opacities, a tree-in bud pattern or any of the 68 imaging patterns listed in Pneumotox. Mediastinal and/or hilar lymphadenopathy characterises those cases with a drug-induced sarcoid-like reaction or an opportunistic infection; for instance, TB in patients receiving TNF-α inhibitors. Pleural effusion or lymph node enlargement can be present as an accompanying feature in severe DILD or pulmonary oedema. Lone free-flowing pleural effusion may occur in isolation as a complication of therapy with 93 different drugs, of which 36 have been associated with eosinophilic pleural effusion. Effusion may at times correspond to the lupus syndrome with circulating antinuclear antibodies (ANAs). Fatty mediastinal deposits, usually asymptomatic, suggest a history of corticosteroid therapy. Acrylate cement or fluid mercury embolism may manifest with dense branched vascular densities on unenhanced CT. Cystic lung lesions with or without pneumothorax can complicate the therapy of malignancies in the chest with chemotherapy or targeted agents. Pulmonary vein stenosis and pericardial effusion following catheter ablation for atrial fibrillation can be evidenced using ultrasound, contrast CT and ventilation/perfusion scan. Patterns that are suggestive of the iatrogenic aetiology (eye-catching patterns) are specifically listed in Pneumotox.

Pulmonary function

Pulmonary function is variably impacted in IRD, depending on both the location of the reaction to the lung parenchyma, airways, pleura or circulation and severity. Reduction of T_{LCO} can be observed in asymptomatic patients exposed to bleomycin, chemotherapeutic agents, amiodarone or ICIs. Monitoring is indicated by existing guidelines. These changes may not predict the development of overt pulmonary toxicity and there may be a risk of unnecessarily harmful treatment interruption.

Fibreoptic bronchoscopy and BAL

Gross bronchoscopy can be useful to diagnose pill aspiration and associated damage to tracheobronchial mucosa. BAL is generally indicated in DILD to rule out an infection, particularly with *Pneumocystis jirovecii*, *Mycobacterium tuberculosis*, viruses or opportunistic microorganisms, using appropriate stains, cultures and molecular techniques. BAL may indicate which cell type (*i.e.* lymphocytes, eosinophils or neutrophils) is increased, or whether atypical alveolar cells or foamy phospholipid-laden macrophages are present. BAL may specifically help diagnose methotrexate pneumonitis, drug-induced eosinophilic pneumonia, amiodarone pulmonary toxicity, ‘chemotherapy lung’ and exogenous lipoid pneumonia. Free mineral lipids in the BAL supernatant and/or stainable lipid vacuoles in alveolar macrophages in BAL fluid or sputum characterise exogenous lopoid penumonia. Elevated BAL cell numbers and fractions tend to normalise upon drug withdrawal as patients improve.

Pathology

Drugs may cause virtually any known ILD pattern including: cellular or fibrotic nonspecific interstitial pneumonia; eosinophilic pneumonia; organising pneumonia; DAD; granulomatous ILD; alveolar haemorrhage; pulmonary vasculitis or capillaritis; desquamative, giant cell or lymphocytic interstitial pneumonia; a usual interstitial pneumonia pattern; a pulmonary alveolar proteinosis pattern; or diffuse pulmonary calcification. However, only a few patterns are specific for the drug aetiology, including phospholipidosis and amiodarone, exogenous lipoid pneumonia, foreign body reactions, fluid silicone or cement embolism, and pill aspiration. While examination of a lung biopsy specimen may help eliminate aetiologies other than the drug, including an infection, a risk–benefit analysis is not available and the attrition from conventional biopsy techniques is not negligible. Therefore, a conservative approach is often chosen, pending the result of the 'de-challenge'.

Other tests

Identification and quantitation of drug levels in plasma can be helpful to diagnose adverse effects from salicylate, opiates, opioids, cocaine, levamisole, cannabinoids or paraquat. Out of range coagulation studies may point to anticoagulant or superwarfarin poisoning. Characterisation of peak wavelength absorbance may confirm methaemoglobinemia or carbon monoxide poisoning. *In vitro* testing of monocyte migration in the presence of the drug or a drug metabolite has been widely used to support the diagnosis of DIRD. Problems with standardisation among laboratories and discrepant results of the test compared with actual re-challenge have not led to wide acceptance of the test. Depending on the clinical pattern of involvement and the suspected drug, evaluation and follow-up of ANA, or perinuclear or cytoplasmic ANCA (anti-MPO and/or anti-PR3) can be useful to document drug-induced lupus, or levamisole-, hydralazine- or propylthiouracil-induced vasculitis. KL-6 has been tested mainly in Japan. The test separates DILDs from ILDs of other aetiologies.

Patients who carry *CYP2C* and *VKORC1* variant alleles may be at risk of developing acenocoumarol-induced or cocaine-induced diffuse alveolar haemorrhage (DAH), or ILD, respectively. A variant in *XPNPEP2* has been associated with ACE inhibitor-induced angio-oedema, and polymorphisms in *BDKRB2* and *ABO* with ACE inhibitor-induced cough.

Ultrasound and measurement of pulmonary and right-sided haemodynamics are indicated in patients with iatrogenic pulmonary hypertension or cardiotoxicity.

Diagnosing DIRD

DIRD diagnosis rests on the following.

- A high degree of suspicion in all patients at all times, regardless of the clinical presentation. Early suspicion may help to avoid continued exposure and progression of respiratory injury.
- Comprehensive drug history, addressing therapy drugs, recreational substances, slimming agents and procedures even if remote in time. Interviewing patients more than once may be needed and checking exposure with the family, relatives or pharmacy can be fruitful in the obtund and those in the intensive care unit (ICU).
- Evaluation of daily dose and dosage of drug (for nitrosoureas, cyclophosphamide, amiodarone and ICIs), measurement of drug levels in plasma (mTOR inhibitors and aspirin), and detection of opiates, synthetic opioids and cannabinoids may refine causality assessment and/or have specific forensic relevance in drug overdoses and fatalities.

- Appropriate timing of exposure *versus* clinical, physiological, imaging or other evidence for respiratory injury. Time to onset may be minutes in drug-induced anaphylaxis, acute bronchospasm or pulmonary oedema; days, weeks or months with most DILD; and years with chronic DILD and fibrosis. Triggers (viruses, drug–drug interactions, surgical intervention, airway manipulation or exposure to oxygen) for the onset of an adverse reaction to a drug that has been taken for many years often remains a mystery. Delayed adverse effects from chemotherapy, amiodarone, immune checkpoint inhibitors and irradiation may manifest weeks, months or years after cessation of exposure.
- Coherence between a specific drug and the clinical, imaging and, sometimes, pathological presentation. Biomarkers of interest include coagulation studies, autoantibodies (ANA and ANCA), specific biomarkers of ICI-related adverse effects, cardiac biomarkers (N-terminal pro-brain natriuretic peptide and troponin) or muscle damage (creatine kinase).
- Careful review of adverse effects of the specific drug on other organs including the liver, kidney and endocrine system. Amiodarone, nitro drugs including nitrofurantoin, statins, TNF-α antagonists and ICIs require particular attention in this respect.
- Exclusion of other possible causes for the observed clinical pattern, including incidental opportunistic infections, respiratory manifestation of the basic disease, progression of an underlying malignant condition, cardiotoxicity or incidental conditions.
- Effect of discontinuation of the suspected drug (to be decided with a multidisciplinary discussion). Causality is supported when drug withdrawal translates into betterment or resolution of signs and symptoms. Corticosteroid therapy is reserved for cases with notable respiratory involvement impacting gas exchange, preferably once the effect of drug withdrawal has been evaluated. Where drug withdrawal is not followed by improvement and conditional upon exclusion of an infection, corticosteroid therapy or a lung biopsy is considered. The beneficial effects of corticosteroid therapy are not specific for the drug aetiology.
- Although this is a convincing criterion for causality when followed by relapse, re-challenging patients with the drug is rarely performed for diagnostic purposes because of the risk of severe relapse. The current view is to reserve re-challenge for cases with low probability of a relationship with the drug and/or when there is no substitute for the drug. Stepwise increases in drug dosage and performing re-challenge in the hospital are advisable.

Clinical presentations

Presenting symptoms include dyspnoea, a nonproductive cough, wheezing, rigours, fever, hoarseness, chest pain, crackles and cyanosis. Severe presentations include hypoxaemia, carbon dioxide retention, dense ILD, bronchospasm, angio-oedema, cardiovascular collapse or shock, massive haemoptysis, or cardiorespiratory arrest. Nonrespiratory features may include a cutaneous rash or discolouration, peripheral and/or mediastinal lymph-node enlargement, myositis, livedo, skin necrosis and/or deep-seated organ involvement. Some patients present with the clinical, imaging and laboratory features of drug lupus, granulomatous polyangiitis, eosinophilic granulomatosis with polyangiitis, myasthenia or myositis.

Severity also depends on acuteness of presentation, extent, location of the reaction, and reversibility upon drug discontinuation and/or under the influence of therapy.

Parenchymal lung disease

Acute pneumonitis/ILD

The prototype acute pneumonitis/ILD is methotrexate pneumonitis when methotrexate is used to treat rheumatoid arthritis or inflammatory bowel disease. The presentation can be fulminant. A similar presentation is possible from 150 other drugs including amiodarone, azacytidine, fludarabine, ICIs, mTOR inhibitors or nitrofurantoin. Acute DILD usually develops with no forewarning symptoms. A background of pre-existing ILD is a possible risk factor. The disease manifests with dry cough, fever, dyspnoea and diffuse pulmonary infiltrates progressing to diffuse white-out on imaging and hypoxaemic respiratory failure. Lymphocytes may dominate and no *Pneumocystis* or other organism is found in the BAL. Corticosteroids are indicated once an infection has been ruled out, often using the *i.v.* route, particularly in intubated patients, to be switched to oral corticosteroids after a few days, then prudently tapered over one or a few months. Drug-induced pneumonitis may follow a less severe a course with discrete pulmonary opacities and no or moderate hypoxaemia (with 323 specific drugs). Rarely does pulmonary fibrosis follow an episode of acute DILD, except if pre-existing rheumatoid lung was present.

Pulmonary infiltrates and eosinophilia

Pulmonary infiltrates and eosinophilia (PIE) is a relatively common reaction that has been described with 190 specific drugs, mainly NSAIDs, antibiotics (minocycline and daptomycin), abused substances, tobacco smoke (especially if of recent onset) and electronic nicotine delivery system vaping. Bilateral shadowing on imaging, peripheral and/or BAL eosinophilia, and an occasional cutaneous rash are present. The disease usually wanes with drug discontinuation and corticosteroid therapy in a manner similar to the aforementioned pattern. Relapse typically occurs if patients are re-challenged. Peripheral eosinophilia may precede clinical and radiographic evidence of relapse. ~50 drugs can produce the more severe variant, acute eosinophilic pneumonia, with pleural effusion and acute respiratory failure requiring mechanical ventilation or ECMO. In any PIE case, other possible causes including parasitic infestation must be ruled out because corticosteroid therapy may promote parasitic superinfection. Cutaneous rash alongside deep-seated organ and neurological involvement indicate DRESS.

Amiodarone pulmonary toxicity

APT is a distinctive condition that typically develops insidiously weeks or months into treatment with this antiarrhythmic in 1.5–3% of patients so treated. Both the incidence and prevalence of APT remain significant. Higher dosage, advancing age and postoperative status increase the risk of developing the condition. APT can be in the form of asymmetrical areas of homogenous or patchy, lobular ground glass or consolidation that may be electron-dense on HRCT because of the two iodine atoms on the amiodarone molecule. Liver can also exhibit increased Hounsfield numbers. Pulmonary function is restrictive in nature with decreased T_{LCO} and hypoxaemia in excess of what is seen in uncomplicated HF, which can be present concomitantly. Foamy macrophages in the BAL, a hallmark of exposure, are not formally diagnostic of APT. Lymphocytosis in the BAL indicates more rapid onset and progression, and efficacy of corticosteroids. Other presentations include unilateral involvement, alveolar haemorrhage, lung nodules, a mass (known as amiodaronoma), masses with decreased attenuation in the centre, pleural effusion, or concomitant involvement of the skin, eye or thyroid. Withdrawal of the drug may not suffice for APT to resolve, due to the high affinity and persistence of amiodarone in the lung. Corticosteroid therapy is often required to accelerate recovery. The fatality rate is between 10% and 40% depending on severity and context. Acute APT may develop in patients on high amiodarone dosages, or following cardiac or thoracic surgery in patients on amiodarone preoperatively or who were started on amiodarone postoperatively. Intra/perioperative oxygen therapy may play a triggering role. Although corticosteroids can be efficacious, overall prognosis in APT/ARDS is guarded.

Pulmonary oedema (noncardiac or cardiac)

Noncardiac pulmonary oedema can be caused by >200 drugs, including chemotherapeutic agents (taxanes and gemcitabine), contrast agents, blood products, tocolytic agents, *i.v.* heroin, hydrochlorothiazide and aspirin. Severity ranges from mild and transient pulmonary infiltrates relapsing upon re-administering the drug to acute pulmonary oedema with a frothy, protein-rich cone of fluid at the mouth and ARDS. For those patients with haemodynamic monitoring, pulmonary capillary wedge pressure is in the normal range.

Cardiogenic pulmonary oedema is an increasingly recognised complication of drugs, mainly anthracyclines, trastuzumab and ICIs, among 40 other drugs.

Chemotherapy lung

Early chemotherapy lung takes the form of a diffuse haze consistent with pulmonary oedema or DAD and is closely associated with administration of bleomycin, busulfan, cyclophosphamide, gemcitabine, nitrosourea or taxanes. Incidence and evidence implicating TKIs (cetuximab, erlotinib, gefitinib and pemetrexed) are country dependent and wide ranging. On pathological examination, modest interstitial inflammation, interstitial oedema, a reactive epithelium and hyaline membranes can be present. Early drug discontinuance and corticosteroid therapy may improve outcome. Still, some patients do progress to ARDS and still others develop slowly progressive pulmonary fibrosis.

The distinctive ICI-induced pulmonary complications are nonspecific ILD, organising pneumonia, sarcoid-like reaction, ARDS, cardiovascular toxicity, and systemic reactions including myasthenia gravis or acute myositis. Guidelines are available to monitor patients on ICIs and treat the complications. Treatment includes corticosteroid therapy and in refractory cases, infliximab, mycophenolate, cyclosporine, secukinumab, tocilizumab or *i.v.* immunoglobin.

Organising pneumonia

Clinically, and on imaging and pathology, drug-induced organising pneumonia (DIOP) may resemble cryptogenic organising pneumonia or organising pneumonia from other causes. DIOP can be in the form of stationary or migratory consolidation, mass or masses, and less often, diffuse shadowing and acute respiratory failure. Organising pneumonia is diagnosed on pathology, on the basis of young connective tissue (alongside foamy cells in amiodarone-induced organising pneumonia) in distal airspaces. Yet, more cases with consolidation on imaging while receiving drugs are now considered as having DIOP, or ‘organising pneumonia *sine* pathology’. As with most so-called histospecific imaging patterns, this is likely to be an overstatement. Deriving management and corticosteroid therapy (which can be justified in authentic DIOP) based on imaging-derived pathology patterns can be misleading. 111 drugs are capable of causing organising pneumonia (mainly amiodarone, antineoplastic chemotherapy, crack cocaine, ICIs, rituximab, statins, and chest or breast radiation therapy). 16 can cause the more severe acute fibrinous organising pneumonia variant. Although drug withdrawal can lead to improvement, corticosteroid therapy is indicated for those patients with severe presentations and/or hypoxaemia, or following equivocal results of drug withdrawal. Failure to recognise the drug aetiology and to discontinue that drug may expose patients to progression or sequential relapses, in spite of baseline corticosteroid therapy. Relapse or relapses concomitant with corticosteroid tapering are a possibility, particularly with amiodarone- or ICI-induced organising pneumonia. Patients who develop DIOP as the result of ICIs are often given corticosteroid therapy early, since waiting for weeks or more for the hypothetical resolution of organising pneumonia after drug withdrawal may increase the risk of progression of the underlying malignancy.

Drug-induced sarcoid-like endothoracic involvement

Patients with a history of sarcoidosis are at risk of resurgence of the disease with the use of sarcoidosis-inducing drugs. Drug-induced sarcoid-like reactions can be subsumed into ILD with a granulomatous component and systemic sarcoid-like reactions with or without involvement of the lung, endothoracic lymph nodes and/or other organs. Drug-induced sarcoid-like reactions may manifest with hypercalcaemia. 35 drugs can produce ILD with a granulomatous component (bacille Calmette–Guérin therapy, TNF-α antagonists, interferons, methotrexate and abused substances containing silica, crospovidone, talc or starch). On imaging, cases may exhibit a miliary or tree-in-bud pattern corresponding to widespread granulomas. Main causal agents for systemic sarcoid-like reactions include TNF-α inhibitors (adalimumab, etanercept and infliximab), interferons, and recently ICIs, among a total of 40 specific drugs. Positron emission tomography is indicated in patients on ICI to ascertain sarcoid-like reaction *versus* the underlying malignancy. Should the diagnosis need confirmation, a needle biopsy can be justified, particularly when it is deemed necessary to rule out progression of malignancy or an infection.

Diffuse alveolar haemorrhage

Drug-induced DAH can be suspected in patients presenting with haemoptysis, a drop in Hb and/or the presence of circulating ANCA. The condition is best diagnosed when gross examination of the BAL exhibits increasingly blood-stained return on sequential aliquots. Causal agents include anticoagulants, superwarfarin rodenticides, antiplatelet agents, direct oral anticoagulants, thrombolytic agents, amiodarone, propylthiouracil and cocaine, among 140 other drugs. DAH can be with or without anti-PR3 or -MPO ANCAs, or both, or anti-glomerular basement membrane antibodies, and with or without pulmonary capillaritis, although very few patients now undergo lung biopsy. Propylthiouracil, levamisole, hydralazine and cocaine may mimic naturally occurring granulomatosis with polyangiitis.

Drug-induced pulmonary fibrosis

>80 drugs have been associated with interstitial pulmonary fibrosis. The most convincing association is with amiodarone, alkylating chemotherapy (busulfan, cyclophosphamide and nitrosoureas), bleomycin, nitrofurantoin, paraquat, radiation therapy and tobacco smoke. A drug-induced mimic of idiopathic pulmonary fibrosis (IPF) with honeycombing is uncommon. As drugs may cause exacerbation of IPF, a drug history is indicated in every IPF patient whose condition is deteriorating. Drug withdrawal is indicated although this rarely translates into tangible improvement.

Drug-induced airway involvement

Angio-oedema with narrowing of the central airway is a relatively common and potentially life-threatening complication of treatments with ACE inhibitors, alteplase or

115 other drugs. Angio-oedema has been more commonly described in middle-aged or elderly African-American women, but any patient in any country is potentially at risk. Drug-induced angio-oedema may develop within hours of the first administration of the drug or occur months or years into an otherwise uneventful treatment. It presents as rapidly progressive breathing difficulty and stridor, which, in severe cases, can cause suffocation, asphyxia and death. Patients may report a history of previous angio-oedema, which may have gone unnoticed. The oedema may localise or predominate on the lips, tongue, mouth floor, arytenoids and laryngeal area, with the thoracic trachea usually being spared. The annual incidence in the population exposed to ACE inhibitors is ~1%, which makes it a significant cumulative lifetime risk in patients so treated. Some patients develop angio-oedema after airway manipulation or intubation. ~40% of the patients with angio-oedema due to ACE inhibitors are admitted to the ICU where mechanical ventilation is indicated in 10–30%. Early diagnosis, identification of the drug aetiology, and maintenance of airway patency are essential since if and when the disease progresses, orotracheal intubation may prove impossible because oedema may occlude the airway lumen. Short of stabilising the airway early, intubation or tracheostomy can be required, with significant risk of asphyxia when performed emergently. Although patients may improve with drug discontinuation, the pharmacological armamentarium in severe or progressive cases may reverse angio-oedema (fresh frozen plasma, C1 esterase inhibitor, ecallantide or icatibant). Close follow-up is necessary, as rebound can occur in the first 24–48 h and discharge must be supervised cautiously. Patients must not be re-exposed to any ACE inhibitor to avoid relapse. Sadly, a fraction of angio-oedema patients will take these medications again, with harmful or fatal consequences. Angiotensin receptor II blockers should be given with caution, as in a few patients, angio-oedema will recur.

~195 drugs can cause mild to moderate bronchospasm, including topical eye drops. Catastrophic, life-threatening bronchospasm may result from exposure to as little as one tablet of NSAID, salicylate or nonselective β-blocker among a total of 46 drugs. The episode can develop within minutes, with a predilection for aspirin-sensitive individuals, atopics and previously known asthmatics. ~15% of all ICU-admitted asthma attack cases may be triggered by drugs. Recent evidence points to insufflated heroin as a trigger of severe asthma attacks and a drug screen can be indicated. Re-challenge is risky, as this would almost inevitably lead to relapse with the risk of prolonged down time and hypoxic brain damage.

Lone, chronic, annoying cough is a classic complication of ACE inhibitors (among 62 drugs). Incidence depends on which ACE inhibitor is used. When in doubt, discontinuation is indicated and the cough will remit in a few days or weeks.

Rare cases of obliterative bronchiolitis have been reported during or following therapy with penicillamine, gold salts or mesalazine. In retrospect, these cases may reflect progression of rheumatoid arthritis- or inflammatory bowel disease-related airway involvement. Obliterative bronchiolitis has been observed in Asia following intake exposure to *Sauropus androgynus* shrub leaf. Recently, rituximab has been cited as the origin of obliterative bronchiolitis.

Pleural pathology

93 agents have been shown to cause subacute/chronic pleural effusion, including arsenic trioxide–all-*trans* retinoic acid, amiodarone, chemotherapeutic agents, ergolines, bosutinib, dasatinib, interleukin-2, glitazones, nitrofurantoin and chest radiation therapy. Involvement is in the form of a free-flowing exudate with or without eosinophilia, a serosanguineous effusion or pleural thickening. Lupus-inducing drugs (etanercept, infliximab, adalimumab and interferons) can cause pleuritis, pleural or pleuropericardial

effusion, and circulating ANA. Anti-double-stranded DNA antibodies are sometimes present. Signs, symptoms and ANA usually resolve upon discontinuation of the drug. Ergots are notable for the insidious development of bilateral pleural thickening with or without an effusion, causing breathlessness, chest pain, an audible friction rub and restrictive lung dysfunction. There is slow and incomplete improvement upon discontinuation. Recently, chemotherapy drugs, mainly cyclophosphamide, have been associated with the development of pleuroparenchymal fibroelastosis, severe restrictive lung dysfunction, pneumothorax, hypercapnic respiratory failure and platythorax, which can be fatal.

Pulmonary vasculopathy

Iatrogenic pulmonary hypertension may follow treatments with amphetamine-like anorectics (fenfluramine and benfluorex), dasatinib and posatinib. Pulmonary hypertension in drug abusers may stem from stimulant (amphetamine) abuse or from repeated *i.v.* injections of crushed tablets intended for oral use, causing obliterative vasculopathy in the long term. Pulmonary hypertension has been reported following catheter ablation for atrial fibrillation. Cases of cyclophosphamide-, gemcitabine-, mitomycin- and nitrosourea-associated pulmonary veno-occlusive disease have been reported.

Methaemoglobinaemia.

Methaemoglobin is a ferric (Fe^{3+}) instead of the normal ferrous (Fe^{2+}) state of Hb that can be formed under the influence of oxidising drugs and chemicals. Neonates are at risk because of their less efficient reductive systems. One to four iron ions in haem can be oxidised into the Fe^{3+} state. Fully oxidised haem ($4Fe^{3+}$ instead of $4Fe^{2+}$) is unable to bind and carry oxygen. Normally, methaemoglobin accounts for <2% of total Hb. Life-threatening or fatal methaemoglobin levels are >40%. The clinical presentation is slate-grey, oxygen-resistant cyanosis; a chocolate-brown hue of the blood; lack of change in colour when blood is exposed to air or oxygen on filter paper or bubbled with oxygen (contrasting with normal venous blood); a low pulsed S_{pO_2}; and a normal measured (dissolved) P_{aO_2} and calculated S_{aO_2}. Methaemoglobin is produced under the influence of benzocaine, dapsone, nitrites, amyl or butyl nitrite, nitric oxide, or foods, among 75 specific agents. Treatment is with *i.v.* methylene blue, to be repeated until methaemoglobin returns to normal. In refractory cases, hyperbaric oxygen or blood exchange can be required.

Disordered breathing during sleep

Disordered breathing during sleep is a recently described area of interest. A history of exposure to baclofen, gabapentin, opiates, pregabalin and ticagrelor should be taken.

Lone breathlessness

~20 separate drugs, including antiplatelet agents (ticagrelor) and hydrochlorothiazide, can produce lone, annoying, otherwise unexplained dyspnoea. This will respond to drug interruption.

Corticosteroid therapy

Corticosteroid therapy is widely prescribed to treat DIRD and it is sometimes advised to prevent amiodarone pulmonary toxicity or the chemotherapy lung from developing. The beneficial, if not life-saving, role of corticosteroid therapy is supported by clinical experience and by many DILD case reports due to bleomycin or amiodarone, in eosinophilic pneumonia and other ILD. In many case reports, corticosteroid therapy was initiated at the time drug was discontinued and the respective merit of each measure cannot be ascertained. Although mentioned in some guidelines, there is no evidence favouring dosage or duration of corticosteroid therapy. As regards acute severe DILD and ARDS, there is also no evidence to support the recent trend of using very high corticosteroid dosages (*e.g.* 1000 mg methylprednisolone for 3 days) *versus* more conventional dosages (*e.g.* 120 mg methylprednisolone twice daily for 3 days, to be tapered using oral corticosteroid therapy). Considering the literature, a suggested regimen for the management of drug-induced ILD of moderate severity may be daily 50–60 mg prednisolone equivalent intradermally in men and women, respectively, to be tapered over 1–3 months. Longer duration of treatment up to 6–18 months may be required in patients with APT to avoid relapse or multiple relapses. Prevention of metabolic disturbances, preemptive therapy against *Pneumocystis*, workup for latent TB infection, monitoring of $CD4^+$ lymphocyte counts, regular attempts at lowering corticosteroid dosage and regular exercise should be part of the management of any corticosteroid therapy. There is little evidence in the literature for a beneficial effect of corticosteroid therapy in exogenous lipoid pneumonia and no evidence in pulmonary oedema. Corticosteroid therapy has no reported role in drug-induced angio-oedema, particularly in light of the novel therapies available to treat that condition.

Conclusion

Drug-induced respiratory involvement is multifaceted, ranging from the benign symptoms of lone cough or dyspnoea to impending respiratory failure. DIRD can be life-threatening, requiring prompt identification, immediate drug withdrawal (with consideration for the treatment of the underlying condition) and expeditious lifesaving management. Invasive techniques should be postponed pending the results of drug withdrawal. Measures including education should be implemented to avoid inadvertent re-exposure to the causal agent. This will hopefully reduce the negative impact of iatrogenic respiratory disease.

Further reading

- Benveniste MF, *et al.* (2019). Recognizing radiation therapy-related complications in the chest. *Radiographics*; 39: 344–336.
- Bernstein JA, *et al.* (2017). Angioedema in the emergency department: a practical guide to differential diagnosis and management. *Int J Emerg Med*; 10: 1.
- Boyer EW (2012). Management of opioid analgesic overdose. *N Engl J Med*; 367: 146–215.
- Camus P. Pneumotox version 2.2. www.pneumotox.com. Date last updated: May 9, 2019.
- Ciottone GR (2018). Toxidrome recognition in chemical-weapons attacks. *N Engl J Med*; 378: 1611–1620.
- Schwaiblmair M, *et al.* (2012). Drug induced interstitial lung disease. *Open Respir Med J*; 6: 63–74.

Radiation-induced lung disease

Peter van Luijk and Robert P. Coppes

Radiotherapy plays an important role in the treatment of tumours located in the thoracic area. The cure rate for these tumours is, however, limited by the low radiation dose that can be tolerated by the lungs. The presently set dose limits (*e.g.* mean dose <20 Gy) already result in pulmonary complications in about one-fifth of patients treated for intrathoracic tumours.

The primary insults after radiation of the lungs seem to be vascular remodelling and an early inflammatory response termed radiation pneumonitis. These are followed by a late fibroproductive phase (figure 1). All these pathologies may lead to compromised lung perfusion, increased vascular resistance, reduced gas-exchange interface between the air and blood, and suboptimal blood oxygenation. Symptoms range from dyspnoea on effort to respiratory failure, oxygen dependency, right heart failure and death.

Almost immediately after irradiation, loss of endothelial cells causes vascular oedema and remodelling. This leads to pulmonary hypertension and right ventricle hypertrophy. Next to this, several inflammatory responses contribute to radiation pneumonitis. Acute alveolar and interstitial inflammation and loss of type I epithelial cells induce proliferation of type II epithelial cells. This leads to a cascade of induction of inflammatory cytokines (figure 1), potentially aggravated by chemotherapeutic agents. Subsequently, an influx of inflammatory cells, such as leukocytes, lymphocytes, neutrophils and macrophages, is induced. Though macrophages are a hallmark, T-lymphocytes and mature dendritic cells also play an important role in radiation pneumonitis.

Radiation-induced lung disease is a consequence of:

- loss of endothelial and type I epithelial cells
- malfunction of the microvasculature
- inflammatory responses
- lung fibrosis

Key points

- Radiotherapy for tumour treatment results in pulmonary complications in ~20% of patients.
- Radiation-induced lung injury involves vascular damage leading to pulmonary hypertension and develops from an early, inflammatory phase to a late, fibrotic phase.

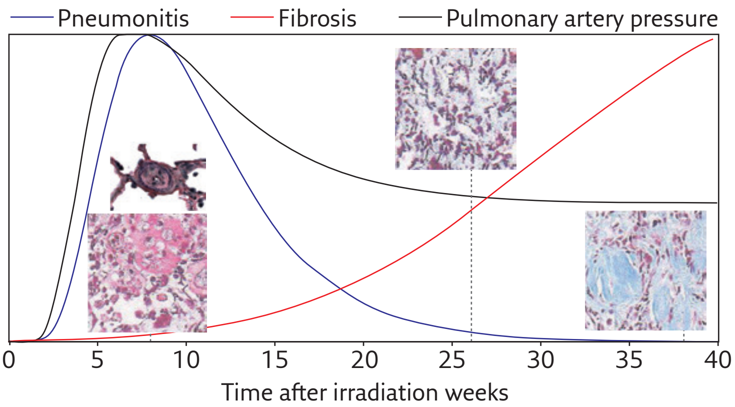


Figure 1. Radiation-induced lung injury develops in an early vascular damage and inflammation phase, and a late fibrotic phase.

Increased vascular permeability with protein exudation contributes to the development of radiation pneumonitis. Depending on the irradiated region and volume, the damaged pulmonary blood vessels (low dose and large volumes) or inflammatory parenchymal damage (high dose and low volumes) affect lung function to induce complications.

Following or even without prior symptomatic pneumonitis, chronic radiation-induced pulmonary fibrosis may develop depending on the irradiated lung volume. Consequently, the presentation of toxicity associated with radiotherapy treatment may vary with the technology used. Radiation fibrosis is caused by accumulation of collagen and other extracellular matrix fibres in the interstitium under persistent cytokine stimuli in combination with arteriocapillary sclerosis.

It should be noted that there are other causes of occupationally induced radiation lung disease; for example, resulting from nuclear accidents, and radon and uranium exposure (see Further Reading).

Further reading

- Abu-Qare AW, *et al.* (2002). Depleted uranium – the growing concern. *J Appl Toxicol*; 22: 149–152.
- Al-Zoughool M, *et al.* (2009). Health effects of radon: a review of the literature. *Int J Radiat Biol*; 85: 57–69.
- Ghobadi G, *et al.* (2012). Lung irradiation induces pulmonary vascular remodelling resembling pulmonary arterial hypertension. *Thorax*; 67: 334–341.
- Göransson Nyberg A, *et al.* (2011). Mass casualties and health care following the release of toxic chemicals or radioactive material – contribution of modern biotechnology. *Int J Environ Res Public Health*; 8: 4521–4549.
- Johnston CJ, *et al.* (2004). Inflammatory cell recruitment following thoracic irradiation. *Exp Lung Res*; 30: 369–382.
- Marks LB, *et al.* (2003). Radiation-induced lung injury. *Semin Radiat Oncol*; 13: 333–345.
- McBride WH, *et al.* (2004). A sense of danger from radiation. *Radiat Res*; 162: 1–19.
- Novakova-Jiresova A, *et al.* (2007). Changes in expression of injury after irradiation of increasing volumes in rat lung. *Int J Radiat Oncol Biol Phys*; 67: 1510–1518.

- Rodemann HP, *et al.* (1995). Cellular basis of radiation-induced fibrosis. *Radiother Oncol*; 35: 83–90.
- Rübe CE, *et al.* (2004). Increased expression of pro-inflammatory cytokines as a cause of lung toxicity after combined treatment with gemcitabine and thoracic irradiation. *Radiother Oncol*; 72: 231–241.
- van der Veen SJ, *et al.* (2015). ACE inhibition attenuates radiation-induced cardiopulmonary damage. *Radiother Oncol*; 114: 96–103.
- van der Veen SJ, *et al.* (2016). Decreasing irradiated rat lung volume changes dose-limiting toxicity from early to late effects. *Int J Radiat Oncol Biol Phys*; 94: 163–171.

Eosinophilic diseases

Claire McBrien and Andrew Menzies-Gow

The exact role of the eosinophil in health has yet to be determined. It is believed to play a role in combating helminthic parasitic infections and, in health, eosinophils primarily reside within the gastrointestinal mucosa. Eosinophilic lung diseases cover a wide spectrum of pathology ranging from airways disease, such as eosinophilic bronchitis, to parenchymal disease, such as eosinophilic pneumonia, and systemic diseases, such as hypereosinophilic syndrome (HES) (table 1).

Nonasthmatic eosinophilic bronchitis

Eosinophilic bronchitis is a common and treatable form of chronic cough that was first identified in 1989. Nonasthmatic eosinophilic bronchitis is a condition that presents with a corticosteroid-responsive chronic cough in nonsmokers. These patients have evidence of eosinophilic airway inflammation without the variable airflow obstruction or airway hyperresponsiveness characteristic of asthma.

Eosinophilic bronchitis accounts for 10–30% of cases of chronic cough referred for specialist investigation. Eosinophilic bronchitis is defined as a chronic cough in patients with no symptoms or objective evidence of airflow obstruction, a histamine/methacholine PC_{20} (provocative concentration causing a 20% fall in FEV_1) of $>16\ mg\cdot mL^{-1}$ and >3% sputum eosinophilia.

It is unclear why eosinophilic inflammation leads to asthma in some individuals and eosinophilic bronchitis in others. Studies by Brightling (2006) suggest that the key may be mast cell localisation. In asthmatics, mast cells infiltrate airways smooth muscle, resulting in airflow obstruction and hyperresponsiveness. In eosinophilic bronchitis, mast cells infiltrate the airway epithelium, leading to bronchitis and cough.

Anti-inflammatory therapy with inhaled corticosteroids is the mainstay of the treatment of eosinophilic bronchitis. Inhaled corticosteroids produce a significant

Key points

- Eosinophilic lung disease covers a wide spectrum of pathology from airways to parenchymal lung disease.
- Always exclude secondary causes of eosinophilia before diagnosing acute or chronic eosinophilic pneumonia.
- Novel therapies are being introduced for eosinophilia, including tyrosine kinase inhibitors and monoclonal antibodies against interleukin-5.

Table 1. The causes and associations of eosinophilic lung disease

Eosinophilic lung disease	Cause/association
Eosinophilic bronchitis	Unknown
Hypereosinophilic syndrome	Idiopathic Lymphoproliferative variant with clonal expansion of T-cells and IL-5 production Myeloproliferative variant with fusion tyrosine kinase FIP1L1–PDGFRA
Pulmonary eosinophilic syndromes	Acute eosinophilic pneumonia Chronic eosinophilic pneumonia Löffler's syndrome Tropical eosinophilia
Allergic bronchopulmonary aspergillosis	*Aspergillus* proliferation in airway lumen induces Th2-mediated, IgE-driven bronchial inflammation
Eosinophilic granulomatosis with polyangiitis	Eosinophilic vasculitis of small to medium-sized vessels
Drug-induced pulmonary eosinophilia	Antibiotics Antifungals NSAIDs Antiepileptics Antipsychotics Anticoagulants Allopurinol Methotrexate
Helminthic infections	*Ascaris lumbricoides* *Strongyloides* Schistosomiasis Filariasis *Toxocara canis*

Th: T-helper cell; NSAID: nonsteroidal anti-inflammatory drug.

improvement in symptoms as well as fall in sputum eosinophilia. There is no evidence to suggest that any one inhaled corticosteroid is more effective. Data are also not available to guide the dose or duration of inhaled corticosteroid therapy. Logically, antileukotrienes may be of benefit, but this hypothesis has not been tested in clinical trials. In very resistant cases, oral corticosteroids may be required for symptom control.

Little is known about the natural history of the condition, but it can be transient, episodic or persistent unless treated.

Acute and chronic eosinophilic pneumonia

Acute eosinophilic pneumonia presents as an acute febrile illness of <1 month's duration and predominately affects cigarette smokers. The average age at presentation is 30 years, with symptoms of dyspnoea, cough, myalgia and fever. Patients often present with severe type I respiratory failure requiring ventilation. Unlike other pulmonary eosinophilic syndromes, the blood eosinophil count is usually normal. The chest radiograph demonstrates diffuse alveolar and interstitial infiltrates. The diagnosis is confirmed by the presence of a bronchoalveolar lavage

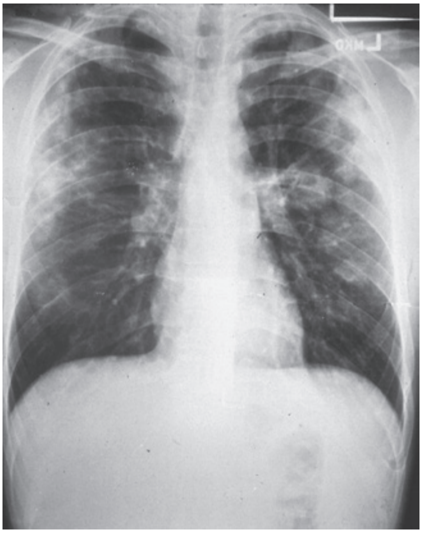


Figure 1. Chest radiograph of patient presenting with chronic eosinophilic pneumonia demonstrating the characteristic peripheral infiltrates.

eosinophilia of >25% in the absence of parasitic, fungal or other infections, and no history of drug hypersensitivity. Acute eosinophilic pneumonia responds quickly to oral corticosteroids, with no relapse after stopping therapy.

Chronic eosinophilic pneumonia typically presents in middle-aged asthmatic females, but it can also develop in nonasthmatic individuals. The symptoms are gradually progressive and include shortness of breath, cough, fever and weight loss. Clinical examination demonstrates wheezing and hypoxia. Patients usually have a raised blood eosinophil count along with elevated inflammatory markers. The majority of patients have infiltrates visible on chest radiography and they are peripherally distributed in about two-thirds of cases (figure 1).

HRCT is more sensitive at demonstrating infiltrates and ~50% of patients also have mediastinal adenopathy. Patients respond well to oral corticosteroids but tend to relapse on discontinuation of therapy. Many patients require long-term, low-dose oral corticosteroids to control the condition; in a small minority, alternative, steroid-sparing agents have been used. This condition is frequently misdiagnosed as asthma. Blood eosinophilia and pulmonary infiltrates respond to corticosteroids within 24–48 h, making it easy to miss this condition if the relevant investigations are not performed prior to starting steroids.

Both acute and chronic eosinophilic pneumonia are idiopathic conditions. It is important to exclude secondary causes of eosinophilia before diagnosing either condition. In clinical practice, this requires a careful travel history, asking about residence in areas of endemic parasitic infection, and a careful drug history including illicit substances. The other main causes of a pulmonary eosinophilic syndrome are allergic bronchopulmonary aspergillosis, HES and eosinophilic granulomatosis with polyangiitis, which should be excluded at the time of diagnosis.

Hypereosinophilic syndrome

HES is a heterogeneous group of disorders characterised by the presence of marked blood and tissue eosinophilia, resulting in a variety of clinical manifestations.

The following criteria are used to define idiopathic HES: blood eosinophilia >1500 cells·mm^{-3} for ≥ 6 months; absence of an underlying cause for the eosinophilia; and end organ damage due to the eosinophilia.

Idiopathic HES can occur at any age but tends to develop in the 30s or 40s, with a male predominance. Nonspecific systemic symptoms are common. More specific symptoms will depend upon which organs are affected. The lungs are involved in ~40% of patients, and present with cough and airflow limitation. Pulmonary function tests demonstrate an obstructive pattern in patients with cough. In patients with cardiac involvement, concomitant pulmonary fibrosis can occur, leading to a restrictive or mixed pattern. The chest radiograph can be normal or demonstrate spontaneously clearing airspace shadowing in early disease. At a later stage, with multi-organ involvement, up to one-third of cases will have diffuse, nonsegmental interstitial infiltrates.

Dulohery *et al.* (2011) reported the frequency of pulmonary HES and associated clinical and radiological features. In their case series of 49 patients, 24% had parenchymal lung involvement, which most commonly consisted of patchy ground-glass opacities and consolidation; one patient exhibited numerous pulmonary nodules. 27% had asthma. Most patients with pulmonary involvement of HES improved and no deaths were observed.

The most important cause of morbidity and mortality in idiopathic HES is cardiovascular involvement. Thromboembolic disease and involvement of the nervous system are also common presentations.

Until recently, oral corticosteroids have been the mainstay of treatment. Better understanding of eosinophil biology has led to the use of more logical targeted therapies. Distinct HES subtypes are now recognised. The myeloproliferative variant is associated with the presence of a fusion tyrosine kinase, FIP1L1–PDGFRA (FIP1-like protein 1–platelet-derived growth factor receptor-α). Historically, these patients had a poor prognosis with poor steroid responsiveness. The use of the tyrosine kinase inhibitor imatinib in this group of patients has significantly improved their outcome.

The lymphoproliferative variant is a consequence of increased production of eosinophilopoietic cytokines by clonal populations of phenotypically abnormal, activated T-lymphocytes. Identification of interleukin (IL)-5 as a key mediator of eosinophilopoiesis led to the use in clinical trials of an anti-IL-5 monoclonal antibody (mepolizumab) for HES. Mepolizumab is an effective corticosteroid-sparing agent in patients with HES negative for FIP1L1–PDGFRA. Mepolizumab response is more likely in those with glucocorticoid-responsive disease.

Further reading

- Allen J (2006). Acute eosinophilic pneumonia. *Semin Respir Crit Care Med*; 27: 142–147.
- Brightling CE (2006). Chronic cough due to nonasthmatic eosinophilic bronchitis: ACCP evidence-based clinical practice guidelines. *Chest*; 129: Suppl. 1, 116S–121S.
- Dulohery MM, *et al.* (2011). Lung involvement in hypereosinophilic syndromes. *Respir Med*; 105: 114–121.
- Klion AD, *et al.* (2006). Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. *J Allergy Clin Immunol*; 117: 1292–1302.

- Kuang FL, *et al.* (2018). Long-term clinical outcomes of high-dose mepolizumab treatment for hypereosinophilic syndrome. *J Allergy Clin Immunol Pract*; 6: 1518–1527.e5.
- Marchand E, *et al.* (2006). Idiopathic chronic eosinophilic pneumonia. *Semin Respir Crit Care Med*; 27: 134–141.
- Reiter A, *et al.* (2017). Myeloid neoplasms with eosinophilia. *Blood*; 129: 704–714.
- Rhee CK, *et al.* (2013). Clinical characteristics and corticosteroid treatment of acute eosinophilic pneumonia. *Eur Respir J*; 41: 402–409.
- Rothenberg ME, *et al.* (2008). Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med*; 358: 1215–1228.

Pulmonary embolism

Mariaelena Occhipinti and Massimo Pistolesi

Despite the advances in prevention and diagnostic imaging, pulmonary embolism (PE) remains a major health problem. The incidence of this pathological condition is as high as one in 1000 per year in the general population. Early diagnosis is fundamental, since early treatment is highly effective. However, due to the low specificity of its clinical presentation, this common disease is still underdiagnosed and it is estimated that in the USA >100 000 people die each year of PE.

Several points will be summarised in this chapter concerning the diagnostic strategies to be adopted in patients with clinical suspicion of PE (table 1). These strategies have been highlighted and brought to the attention of the scientific community by scientific publications, expert reviews and international guidelines.

Pre-test clinical probability of PE

A thorough clinical evaluation is the key step in raising the suspicion of the disease and setting up appropriate diagnostic strategies. The vast majority of patients with PE has at least one of four symptoms which are, in decreasing order of frequency: sudden-onset dyspnoea, chest pain, fainting (or syncope), and haemoptysis. Although the diagnostic yield of individual clinical symptoms, signs and common laboratory tests is limited, the combination of these variables, either by empirical assessment or by a prediction rule, can be used to stratify patients by their increased risk of PE (low, intermediate or high). The results of two broad prospective studies in the 1990s (Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) and Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED)) indicate that physicians' estimates of the clinical likelihood of PE, even if based on empirical assessment, do have predictive value.

Three objective scoring systems have been tested prospectively and validated in large-scale clinical trials: the Wells score, the Geneva score and the Pisa score. The three

Key points

- Although early treatment is highly effective, pulmonary embolism (PE) is underdiagnosed and, therefore, it remains a major health problem.
- Diagnostic strategy should be based on clinical evaluation of the probability of PE.
- The negative and positive predictive values of diagnostic tests for PE are high when the results are concordant with the clinical assessment.
- Additional testing is necessary when the test results are inconsistent with clinical probability.

Table 1. General rules for the diagnostic work-up of patients clinically suspected of PE

Pre-test clinical probability of PE should be objectively assessed in each patient
D-dimer should be determined if pre-test probability of PE is low or intermediate
Diagnostic imaging of the chest should be used to assess post-test probability of PE in most patients; further testing is necessary when post-test probability of PE is neither sufficiently low nor sufficiently high to permit therapeutic decisions
Diagnostic strategies for PE could differ significantly in different clinical contexts and special conditions

scoring systems perform reasonably well to objectively assess the clinical probability of PE in outpatients or emergency room patients. The Pisa score seems to perform better than other scoring systems in hospitalised patients. It appears that fully standardised scoring systems, such as the Wells and Geneva scores, with no implicit evaluation of symptoms (*e.g.* dyspnoea or chest pain) or of simple instrumental findings (ECG or chest radiograph), cannot perform better than the subjective clinical judgement of experienced physicians, as was shown in the PIOPED and the PISA-PED studies. Conversely, interpretation of ECG and chest radiograph in these patients, as requested by the Pisa score, necessitates a certain level of clinical experience and is hard to standardise. The three scoring systems are reported in table 2.

Nevertheless, several prospective studies have shown that, whatever scoring method is used, pre-test clinical probability categorises patients into subgroups with a different prevalence for PE, and the positive and negative predictive values of various objective tests are strongly conditioned by the independently assessed pre-test clinical probability. Accordingly, international guidelines recommend that the clinical probability of the disease should be assessed in each patient with suspected PE before any further objective testing occurs. Future research is needed to develop standardised models, of varying degrees of complexity, which may find application in different clinical settings to predict the probability of PE.

D-dimer

Plasma D-dimer levels are elevated in the presence of simultaneous activation of coagulation and fibrinolysis. A normal D-dimer level has, consequently, a high negative predictive value for PE or deep vein thrombosis (DVT). However, endogenous production of fibrin may be increased in a wide variety of conditions including, among others, cancer, inflammation, infection, pregnancy and chronic illnesses. Elevated plasma D-dimer levels have, for this reason, a low positive predictive value for PE and DVT.

The value of D-dimer measurement in the diagnostic work-up of each patient must be considered according to the determined clinical probability of PE, the sensitivity of the particular method of D-dimer measurement employed, and the patient's age. A negative D-dimer test result, measured by any method, in combination with a low probability by clinical assessment, excludes PE with accuracy. An intermediate clinical probability would also exclude PE with reasonable certainty if D-dimer was measured as negative by a high-sensitivity ELISA method. It has been shown that the 3-month risk of PE or DVT in untreated patients with a negative D-dimer and a low or intermediate clinical probability is <1%. Conversely, if clinical assessment results in high probability for PE, a concomitant negative D-dimer test does not exclude PE. D-dimer levels increase with age, with a consequent decrease in specificity for suspected PE. In the ADJUST-PE study, a multicentre, prospective management study,

Table 2. *Clinical probability scoring systems*

Wells		**Geneva**		**Pisa**
Clinical features	**Points**	**Clinical features**	**Points**	
Signs and symptoms of DVT	3.0	Recent surgery	2	Symptoms
Heart rate >100 beats·min^{-1}	1.5	Previous PE or DVT	2	Sudden-onset dyspnoea
Immobilisation or surgery	1.5	Older age	2	Chest pain
Previous DVT or PE	1.5	Hypocapnia	2	Fainting
Haemoptysis	1.5	Hypoxaemia	2	Chest radiograph findings
Malignancy	1.5	Tachycardia	2	Amputation of hilar artery
PE more likely than an alternative diagnosis	3.0	Plate-like atelectasis	2	Focal oligaemia
		Hemidiaphragm elevation	2	Pleural-based consolidation
Score category				
Low	<2		≤4	None of the above is present, or an alternative diagnosis that may account for their presence is identified
Intermediate	2–6		5–8	≥1 of the above symptoms, alone or with ECG findings of acute right ventricular overload
High	>6		≥9	≥1 of the above symptoms, not explained, and ≥1 of the above chest radiograph findings

using an age-adjusted cut-off instead of the 'standard' 500 mg·L^{-1} cut-off increased the number of patients in whom PE could be excluded from 6.4% to 29.7%, without any additional false-negative findings.

The number of patients with suspected PE in whom D-dimer must be measured to exclude one PE episode ranges between three in the emergency department and ≥10 in hospitalised patients. It thus appears recommendable to consider D-dimer measurement in the diagnostic work-up of PE only in outpatients or in patients of the emergency department with low or intermediate levels of clinical probability.

The sensitivity of D-dimer testing for PE increases with the extent of PE. D-dimer concentrations are the highest in patients with PE involving the pulmonary trunk and lobar arteries and with perfusion scan defects involving >50% of the pulmonary circulation.

Diagnostic imaging of the chest to assess post-test probability of PE

The contribution of CT angiography (CTA) in the diagnosis of PE has greatly increased over the last decade, as a consequence of the extraordinary advancement in CTA technology. Multidetector CTA has become the most widely used technique for the diagnosis or exclusion of PE and has almost replaced lung scanning as a screening test and conventional pulmonary angiography as the reference standard for the diagnosis of acute PE (figure 1). However, CTA does not escape the simple rule that the combined use of the estimated clinical probability and the results of one noninvasive test substantially increases the accuracy in confirming or ruling out a disease, as compared with either assessment alone. As shown by the PIOPED II trial, the predictive value of CTA is high with a concordant clinical assessment, but additional testing is necessary when clinical probability is inconsistent with the imaging results. Several articles have shown a positive yield rate of CTA of <10% in patients who are clinically suspected of PE. This may indicate that the wide availability of CTA has led to an overuse of

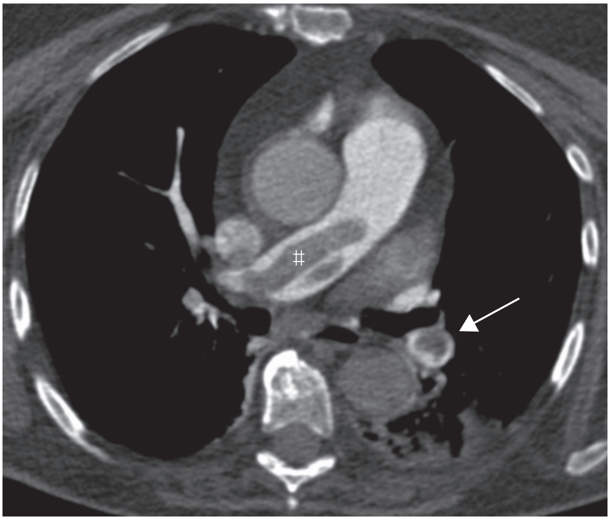


Figure 1. Axial chest CTA with a pulmonary floating thrombus within the pulmonary trunk extending to the right main pulmonary artery (♯) and to the left intralobar artery (arrow). Note the central position of the thrombus within the arteries, not juxtaposed to artery walls, consistent with a recent thrombus.

the technique as a screening procedure for PE in the emergency department. It has been suggested that a substantial number of CTA assessments could be avoided by adhering to the information derived from clinical evaluation and D-dimer testing.

Perfusion (*Q′*) lung scanning was introduced 40 years ago as the first chest imaging method for the diagnosis of PE. A normal *Q′* scan excludes PE (high sensitivity and high negative predictive value), whatever the pre-test clinical probability. However, *Q′* scanning was thought to be poorly specific (low positive predictive value) for PE because all common pulmonary diseases (infections, neoplasms and COPD) can produce decreased blood flow to the affected regions.

Ventilation (*V″*) scanning was added to *Q′* scanning to increase the specificity of scintigraphy. This diagnostic approach is based on the flawed expectation that regions of the lung excluded from perfusion by emboli maintain normal ventilation, thus giving rise to *V″/Q′* mismatch. This criterion to diagnose PE is at variance with the notion that ventilation is shifted away from embolised lung regions. The concept that dead space ventilation is not significantly increased in the course of PE was widely held in respiratory pathophysiology before the *V″/Q′* scanning approach was developed, as was asserted by Comroe (1966), who foresaw that 'decrease in wasted ventilation (ventilation to unperfused or poorly perfused lung) helps the patient but hinders the physician in diagnosis'. This is in keeping with the results of the PIOPED trial, in which it was shown that the high-probability *V″/Q′* scan (*Q′* defects without matching *V″* abnormalities) lacks sensitivity in diagnosing PE since it fails to identify 59% of PE patients (sensitivity 41%, specificity 97%). The combination of clinical probability and *V″/Q′* scan results either confirms or excludes PE in <30% of patients.

The diagnostic value of the *Q′* scan (without *V″* imaging) was reappraised in the PISA-PED study, in which *Q′* scans were read either as compatible with PE when featuring wedge-shaped (segmental) perfusion defects or not compatible with PE when featuring defects other than wedge-shaped or normal perfusion. When compared with the original PIOPED protocol, the PISA-PED approach has several advantages, as follows: 1) *Q′* scanning either confirms or excludes the clinical suspicion of PE (thus virtually eliminating nondiagnostic examinations); 2) the sensitivity of lung scintigraphy is greatly increased (86% *versus* 41%), yet with minor reduction of specificity (from 97% to 93%); and 3) the combination of clinical probability and *Q′* scanning results confirms or excludes PE in ~80% of patients. The diagnostic performance of *Q′* scanning for PE was later confirmed by examining 889 scans from the PIOPED II trial. PIOPED II data were used to test the hypothesis that reading *Q′* scans without *V″* scans, and categorising the *Q′* scan as 'PE present', 'PE absent' or 'nondiagnostic', can result in clinically useful sensitivity and specificity in a high proportion of patients. The study has confirmed that *Q′* scanning and CTA have comparable positive and negative predictive values, with no nondiagnostic readings for the *Q′* scan (table 3). Accordingly, in 2012, the Society of Nuclear Medicine revised the practice guidelines for lung scintigraphy, reporting that 'The modified PIOPED II and PISAPED criteria using information from chest radiograph and perfusion scans have been shown to perform equivalently to those including ventilation scintigraphy, with fewer nondiagnostic studies' (Parker *et al*., 2012).

Diagnostic strategies in different clinical contexts and special conditions

Most clinicians and diagnostic radiologists feel more comfortable with an anatomical demonstration of whether a clot is present than assessing the probability of PE by looking at *V″/Q′* mismatches (PIOPED) or evaluating the shape of a perfusion defect (PISA-PED). Furthermore, contrary to scintigraphy, in most hospitals, CTA is available

Table 3. Predictive values of Q′ scanning and multidetector CTA

Imaging test	PPV	NPV	Nondiagnostic
***Q′* scanning**	85	96	0
CTA	86	95	6

Data are presented as percentages. PPV: positive predictive value; NPV: negative predictive value. Data from retrospective evaluation of PIOPED II data (Sostman *et al*., 2008; Stein *et al*., 2006).

24 h a day, 7 days a week. However, CTA cannot be performed in the whole population of patients suspected of PE. As shown in the PIOPED II trial, ~50% of the recruited patients did not undergo CTA due to documented contraindications, such as renal failure, abnormal creatinine levels, allergy to contrast agent, possible pregnancy, critical illness, requirement of ventilator support, or recent myocardial infarction. In all these conditions, *Q′* scanning could be the preferred alternative approach to the diagnosis of PE. This approach is particularly important for female patients of reproductive age, in whom the breast irradiation dose from CTA can be minimised by using *Q′* scanning as the first imaging test. It has also been shown that contrast medium-induced nephropathy is at least as common after CTA as a diagnosis of PE.

Under circumstances in which clinical probability and imaging test results (CTA or scintigraphy) are discordant, further testing (such as lower limb compression ultrasonography, as shown in figure 2) is required to either confirm or exclude the diagnosis. Another practical approach could be to image the pulmonary circulation with CTA if *Q′* scanning was the first imaging test used, or *vice versa*.

The improvements in radiological accuracy of CTA, achieved with the introduction of more advanced multislice CT scanners and the optimisation of CT protocols, have been coupled with an increased frequency in reported incidental (unsuspected) PE and isolated subsegmental PE. Incidental PE can be found in 3.6% of cancer-staging

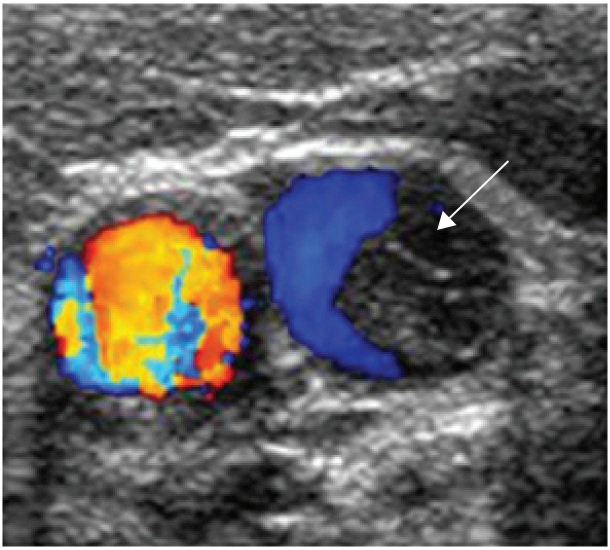


Figure 2. Ultrasound image of DVT. Transverse colour-mode image showing a non-compressible right common femoral vein with echogenic endoluminal thrombus (arrow). Courtesy of Francesco Rosella, University Hospital Santa Maria della Misericordia, Udine, Italy.

CT and 1.1% of all coronary CT scans and, if untreated, has the same prognosis of symptomatic PE with regard to the risk of recurrent venous thrombotic disease and mortality. This observation has warranted the application of similar management decisions for patients with incidental PE as those with symptomatic PE. In cases of isolated subsegmental PE, the clinical significance is still questionable and solid evidence regarding the best method of patient management is still lacking. However, some experts believe that patients should be treated, especially if they have cancer and a proximal clot.

Conclusion

The choice of a diagnostic strategy for PE depends on the pre-test clinical probability of PE, the condition of the patient, the availability of the necessary test, the risks of testing, the risk of an inaccurate positive or negative diagnosis, and the cost. Clinical evaluation makes it possible to classify patients into probability categories corresponding to an increasing prevalence of PE, whether assessed by implicit clinical judgement or by a validated prediction rule. The structured models to assess clinical probability that have so far been developed have different levels of performance in patients of the emergency department compared with those who are hospitalised. Exclusion of PE by clinical probability assessment and D-dimer measurement spares the cost and radiation of an imaging evaluation. CTA has become the method of choice for imaging the pulmonary vasculature when PE is suspected in routine clinical practice. Scintigraphy can be considered as the preferred alternative chest imaging technique for patients with contraindications to CTA. If scintigraphy is used, eliminating the *V*′ scan can reduce cost and radiation load with gain in diagnostic yield.

Further reading

- Comroe JH Jr (1966). The main functions of the pulmonary circulation. *Circulation*; 33: 146–158.
- Eisner MD (2003). Before diagnostic testing for pulmonary embolism: estimating the prior probability of disease. *Am J Med*; 114: 232–234.
- Klok FA, *et al.* (2017). Management of incidental pulmonary embolism. *Eur Respir J*; 49: 1700275.
- Konstantinides SV, *et al.* (2014). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*; 35: 3033–3069.
- Mamlouk MD, *et al.* (2010). Pulmonary embolism at CT angiography: implications for appropriateness, cost, and radiation exposure in 2003 patients. *Radiology*; 256: 625–632.
- Miniati M, *et al.* (1996). Value of perfusion lung scan in the diagnosis of pulmonary embolism: results of the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). *Am J Respir Crit Care Med*; 154: 1387–1393.
- Miniati M, *et al.* (2012). Clinical presentation of acute pulmonary embolism: survey of 800 cases. *PLoS One*; 7: e30891.
- Mitchell AM, *et al.* (2012). Prospective study of the incidence of contrast-induced nephropathy among patients evaluated for pulmonary embolism by contrast-enhanced computed tomography. *Acad Emerg Med*; 19: 618–625.
- Parker JA, *et al.* (2012). SNM practice guideline for lung scintigraphy 4.0. *J Nucl Med Technol*; 40: 57–65.
- PIOPED Investigators (1990). Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). *JAMA*; 263: 2753–2759.

- Pistolesi M (2010). Pulmonary CT angiography in patients suspected of having pulmonary embolism: case finding or screening procedure? *Radiology*; 256: 334–337.
- Remy-Jardin M, *et al.* (2007). Management of suspected acute pulmonary embolism in the era of CT angiography: a statement from the Fleischner Society. *Radiology*; 245: 315–329.
- Righini M, *et al.* (2014). Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. *JAMA*; 311: 1117–1124.
- Sostman HD, *et al.* (2008). Sensitivity and specificity of perfusion scintigraphy combined with chest radiography for acute pulmonary embolism in PIOPED II. *J Nucl Med*; 49: 1741–1748.
- Stein PD, *et al.* (2006). Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med*; 354: 2317–2327.
- Stein PD, *et al.* (2011). Controversies in diagnosis of pulmonary embolism. *Clin Appl Thromb Hemost*; 17: 140–149.
- Tsai J, *et al.* (2012). Correlates of in-hospital deaths among hospitalizations with pulmonary embolism: findings from the 2001–2008 National Hospital Discharge Survey. *PLoS One*; 7: e34048.

Pulmonary hypertension

Jason Weatherald and Marc Humbert

Classification and definitions

Pulmonary hypertension is defined as an increase in the mean pulmonary arterial pressure (mPAP) >20 mmHg at rest during a right heart catheterisation. Assessment of the pulmonary artery wedge pressure (PAWP) further classifies patients as pre-capillary pulmonary hypertension (PAWP ≤15 mmHg) or post-capillary pulmonary hypertension (PAWP >15 mmHg). Pre-capillary pulmonary hypertension is also defined by an elevation in the pulmonary vascular resistance (PVR) ≥3 Wood units (PVR is calculated as (mPAP − PAWP) divided by the cardiac output).

Clinical and haemodynamic characteristics classify pulmonary hypertension into five groups that share similar pathology, clinical characteristics and treatment (table 1). Proper classification is essential to guide the most appropriate therapy.

Group 1 relates to PAH which is defined by pre-capillary pulmonary hypertension (mPAP >20 mmHg, PAWP ≤15 mmHg and PVR ≥3 Wood units). PAH may be idiopathic or be caused by certain drugs and toxins, genetic mutations, or associated medical conditions. Anorexigen drugs such as fenfluramine or benfluorex have been known to cause PAH for

Key points

- Pulmonary hypertension is classified in to five groups based on similar haemodynamics, pathophysiological mechanisms and treatment strategies. Group 1 is pulmonary arterial hypertension (PAH), group 2 is due to left heart disease, group 3 is due to chronic lung disease and hypoxia, group 4 is chronic thromboembolic pulmonary hypertension (CTEPH) and group 5 is multifactorial and unclear mechanisms.
- PAH is a rare disease associated with a poor prognosis. Diagnosis requires right heart catheterisation and exclusion of other causes.
- Treatment of PAH is based on a comprehensive risk assessment. Most patients are treated with combinations of oral medications that have proven benefits in randomised controlled trials. Intravenous prostacyclin analogues should be considered in high-risk patients.
- CTEPH should be excluded in all patients with pulmonary hypertension with a ventilation/perfusion scan. Patients with established chronic thromboembolic disease should be evaluated for pulmonary endarterectomy surgery in expert centres. All patients require life-long anticoagulation and some may benefit from other medical therapies or balloon pulmonary angioplasty.

Table 1. Updated clinical classification of pulmonary hypertension (PH)

1 PAH

- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH
- 1.4 PAH Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blockers
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
- 1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease

- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3 PH due to lung diseases and/or hypoxia

- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung diseases

4 PH due to pulmonary artery obstructions

- 4.1 CTEPH
- 4.2 Other pulmonary artery obstructions (*i.e.* angiosarcoma, arteritis, congenital stenosis)

5 PH with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic and metabolic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, glycogen storage disease, Gaucher disease, thyroid disorders
- 5.3 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental PH
- 5.4 Complex congenital heart disease

LVEF: left ventricular ejection fraction. Reproduced and modified from Simonneau *et al.* (2019).

many years, while more recently alkylating chemotherapeutic agents and dasatinib, a tyrosine kinase inhibitor used in the treatment of chronic myelogenous leukaemia, have been reported to cause PAH. Heritable PAH is most commonly associated with mutations in the bone morphogenic protein receptor II (*BMPR2*) gene, but several other mutations in genes that interact with *BMPR2* signalling have been identified to cause PAH. Associated PAH includes several other conditions, such as congenital heart diseases and connective tissue diseases, which have clinical, haemodynamic and histopathological similarities to idiopathic PAH. Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH) are a spectrum of related diseases that are classified in group 1. They are associated with sporadic or familial genetic mutations in the eukaryotic translation initiation factor 2 alpha kinase 4 (*EIF2AK4*) gene, connective tissue diseases and occupational exposure to organic solvents. PVOD and PCH should be distinguished from other causes of Group 1 PAH because of important pathological differences and the observation that such patients do not respond, and may even worsen, when treated with conventional PAH therapies. Another distinct subgroup of PAH patients will demonstrate an acute improvement in haemodynamics during vasoreactivity testing. These patients are potential long-term responders to calcium channel blockers (CCBs) and such patients may have an excellent long-term prognosis.

Group 2 and group 3 pulmonary hypertension are caused by left heart diseases and chronic pulmonary diseases, respectively. Together group 2 and group 3 are the most common types of pulmonary hypertension. Group 2 is defined by post-capillary pulmonary hypertension (mPAP >20 mmHg and PAWP >15 mmHg) and the presence of left-sided valve disease or left ventricular systolic or diastolic dysfunction. Group 3 pulmonary hypertension has a pre-capillary haemodynamic profile, but in the presence of significant lung disease or chronic hypoxia. CTEPH, group 4, is an important cause of pre-capillary pulmonary hypertension that results from persistent vascular obstruction in the pulmonary arteries despite anticoagulation. Group 5 is pulmonary hypertension due to multiple or unclear mechanisms and includes myeloproliferative neoplasms, haemolytic anaemias, sarcoidosis and other rare diseases.

Pathobiology and pathology

Pulmonary arterial endothelial cell dysfunction, inflammation, vasoconstriction, thrombosis and abnormal vascular proliferation are key processes in the pathogenesis of pulmonary hypertension. In PAH, pulmonary arteries and arterioles exhibit typical histological abnormalities including hypertrophy and hyperplasia of smooth muscle cells in the media, intimal fibrosis, adventitial fibrosis and perivascular inflammation. Mitochondrial dysfunction, altered expression and function of certain growth factors, and immune cell dysregulation play an important role in PAH pathogenesis. The plexiform lesion is the pathological hallmark of PAH characterised by exuberant focal proliferation of endothelial cells with many capillary-like channels and aneurysmal widening (figure 1). They are located in the pre- and intra-acinar pulmonary arteries often near arterial branch points. Thrombosis *in situ* with organisation and incomplete recanalisation causes other vascular abnormalities that resemble the plexiform lesions. Pulmonary arterial remodelling is also observed in patients with group 2 and group 3 pulmonary hypertension. Pulmonary venous changes, particularly venous intimal thickening and medial hypertrophy play an important role in the development of pulmonary hypertension in patients with left heart disease.

Epidemiology and survival

PAH is a rare disease with an estimated prevalence of 15–60 individuals per million population, with an annual incidence of 5–10 cases per million per year in Europe. Approximately half of PAH is due to associated conditions, with connective tissue diseases, particularly systemic sclerosis, being the most frequent. Prior to development of effective therapies for PAH, median survival was 2.8 years in the National Institutes of Health Primary Pulmonary Hypertension registry. Since then, the development of effective therapies has significantly improved survival; however, PAH remains a progressive and fatal disease in most cases. In the French PAH registry, the 3-year overall survival for idiopathic, drug-induced and heritable PAH diagnosed between

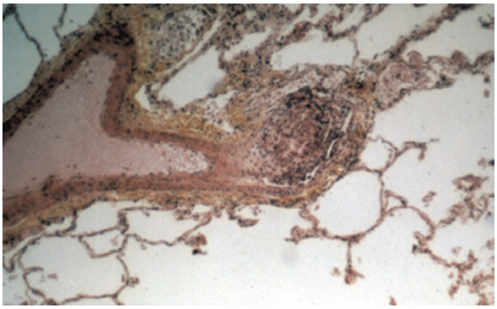


Figure 1. A typical plexiform lesion in a patient with idiopathic PAH. The lesion is located at an arterial branching point.

2006 and 2016 was 72.9%. Mortality is associated with increasing age, male sex, poor functional capacity, low exercise capacity and impaired right ventricular function. A multidimensional risk assessment should be performed regularly in PAH patients. This includes an assessment of symptoms and exercise capacity with New York Heart Association (NYHA) functional class and 6-min walking distance (6MWD), biomarkers, such as N-terminal pro-brain natriuretic peptide (NT-proBNP), and imaging or haemodynamic measures of right ventricular function, in order to predict future risk and guide treatment decisions (table 2).

CTEPH incidence after acute pulmonary embolism ranges from 0.4% to 6.2%, but is probably closer to 0.5% in all-comers and 3.2% in survivors of the acute event. In an international registry, 77% of CTEPH patients had a previous history of pulmonary embolism or deep vein thrombosis. Survival in CTEPH is most strongly related to whether patients undergo pulmonary endarterectomy (PEA) surgery. For patients undergoing pulmonary endarterectomy, 3-year survival was 89% compared with 70% in patients who did not undergo surgery. Pre-operative haemodynamics and comorbid conditions are predictive of survival in CTEPH.

Diagnosis

PAH should be considered in the differential diagnosis of exertional dyspnoea, syncope, angina and/or progressive limitation of exercise capacity, particularly in patients without apparent risk factors, symptoms or signs of common cardiovascular and respiratory disorders. Special awareness should be directed towards patients with associated conditions and/or risk factors for development of PAH, such as family history, connective tissue diseases, congenital heart diseases, HIV infection, portal hypertension, haemolytic anaemia, or a history of drug and toxin intake known to induce PAH. In everyday clinical practice, such awareness may be low. More often, pulmonary hypertension is found unexpectedly on transthoracic echocardiography requested for another indication.

The diagnostic algorithm begins with an assessment of symptoms and signs of pulmonary hypertension and usually an echocardiogram (figure 2). A common scenario is pulmonary hypertension found unexpectedly on transthoracic echocardiography requested for another indication. The tricuspid regurgitation velocity and other echocardiographic signs of pulmonary hypertension can be used to determine the likelihood of disease. A ventilation/perfusion (V'/Q') scan should be performed to exclude CTEPH (group 4) in most patients. If the V'/Q' scan shows multiple segmental or lobar perfusion defects, CTEPH should be considered and a referral to an expert pulmonary hypertension centre should be pursued to confirm the diagnosis and for

Table 2. Risk assessment in PAH

Determinants of prognosis[#] **(estimated 1-year mortality)**	**Low risk <5%**	**Intermediate risk 5–10%**	**High risk >10%**
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[¶]	Repeated syncope[+]
NYHA functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak $V'_{\mathrm{O_2}}$ >15 mL·min^{-1}·kg^{-1} (>65% pred)	Peak $V'_{\mathrm{O_2}}$ 11–15 mL·min^{-1}·kg^{-1} (35–65% pred)	Peak $V'_{\mathrm{O_2}}$ <11 mL·min^{-1}·kg^{-1} (<35% pred)
	$V'_{\mathrm{E}}/V'_{\mathrm{CO_2}}$ slope <36	$V'_{\mathrm{E}}/V'_{\mathrm{CO_2}}$ slope 36–44.9	$V'_{\mathrm{E}}/V'_{\mathrm{CO_2}}$ slope ≥45
NT-proBNP plasma levels	BNP <50 ng·L^{-1}	BNP 50–300 ng·L^{-1}	BNP >300 ng·L^{-1}
	NT-proBNP <300 ng·L^{-1}	NT-proBNP 300–1400 ng·L^{-1}	NT-proBNP >1400 ng·L^{-1}
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2	RA area 18–26 cm^2	RA area >26 cm^2
	No pericardial effusion	No or minimal pericardial effusion	Pericardial effusion
Haemodynamics	RAP <8 mmHg	RAP 8–14 mmHg	RAP >14 mmHg
	CI ≥2.5 L·min^{-1}·m^{-2}	CI 2.0–2.4 L·min^{-1}·m^{-2}	CI <2.0 L·min^{-1}·m^{-2}
	$S_{\mathrm{vO_2}}$ >65%	$S_{\mathrm{vO_2}}$ 60–65%	$S_{\mathrm{vO_2}}$ <60%

$V'_{\mathrm{O_2}}$: oxygen uptake; $V'_{\mathrm{E}}/V'_{\mathrm{CO_2}}$: ventilatory equivalents for carbon dioxide; BNP: brain natriuretic peptide; CMR: cardiac magnetic resonance; RA: right atrium; RAP: right atrial pressure; CI: cardiac index; $S_{\mathrm{vO_2}}$: mixed venous oxygen saturation. [#]: most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated for idiopathic PAH (IPAH) and the cut-off levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk. [¶]: occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient. [+]: repeated episodes of syncope, even with little or regular physical activity. Reproduced from the 2015 ESC/ERS PH guidelines (Galié *et al*. 2015).

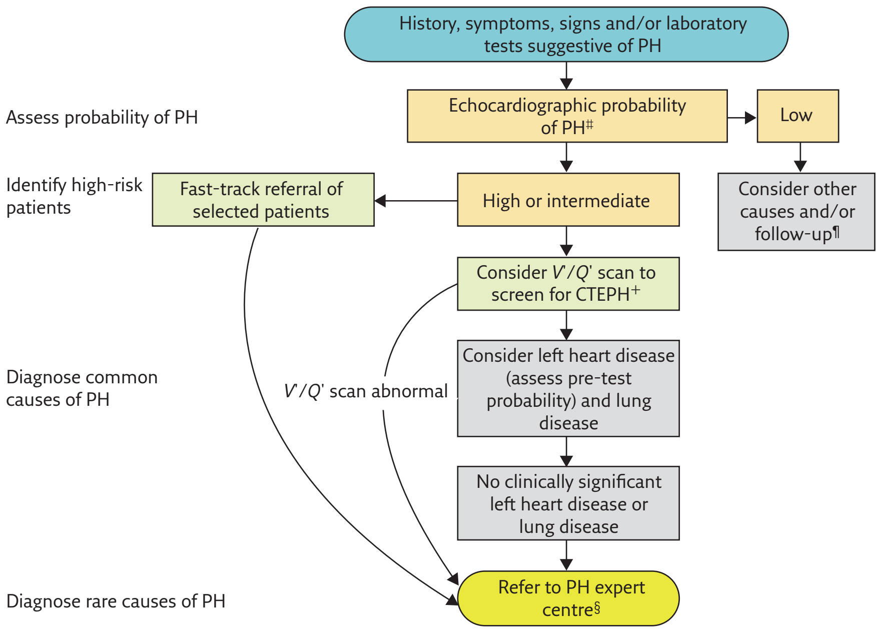

History, symptoms, signs and/or laboratory tests suggestive of PH
Assess probability of PH
Echocardiographic probability of PH#
Low
Identify high-risk patients
Fast-track referral of selected patients
High or intermediate
Consider other causes and/or follow-up¶
Consider V'/Q' scan to screen for CTEPH+
Diagnose common causes of PH
V'/Q' scan abnormal
Consider left heart disease (assess pre-test probability) and lung disease
No clinically significant left heart disease or lung disease
Diagnose rare causes of PH
Refer to PH expert centre§

Figure 2. Algorithm for the diagnosis of pulmonary hypertension (PH) and its causes: triage of urgent cases and diagnosis of common conditions. #: described in the 2015 European Society of Cardiology/European Respiratory Society PH guidelines; ¶: these include chronic thromboembolic disease without PH, which should be considered in patients with risk factors and/or previous venous thromboembolism; +: single photon emission CT or planar V'/Q' scan is acceptable (interpretation is binary: normal or abnormal); §: referral of a patient to be seen in person or for a teleconsultation. Reproduced and modified from Frost et al. *(2019).*

a multidisciplinary assessment for PEA eligibility. Additional evaluation for CTEPH includes a right heart catheterisation, CT pulmonary angiography and conventional selective pulmonary angiography to determine disease distribution and surgical accessibility. Clinical evaluation should focus on the identification of the most common forms of pulmonary hypertension: left heart diseases (group 2) and lung diseases (group 3). Pulmonary function tests, arterial blood gas analysis, nocturnal oximetry, ECG, transthoracic echocardiography and HRCT of the chest are routine investigations. Normal left ventricular systolic function on echocardiography, with severe left atrial enlargement, left ventricular hypertrophy and abnormal diastolic parameters suggests group 2 pulmonary hypertension due to heart failure with preserved LVEF or diastolic dysfunction. The HRCT may suggest features of interstitial lung disease or emphysema, but can also suggest signs of PVOD/PCH such as septal thickening, centrilobular ground glass and mediastinal lymphadenopathy. In patients with minimal or no signs of left heart or lung disease, additional tests for conditions associated with PAH include a HIV test, immunological serology and liver ultrasonography. Referral to a pulmonary hypertension expert centre should be considered early for patients with severe pulmonary hypertension and/or right ventricular dysfunction, or when the degree of pulmonary hypertension on echocardiography is disproportionate to the degree of left heart or lung disease. A right heart catheterisation is mandatory to confirm the diagnosis of PAH or CTEPH before initiating specific therapy and it also provides important prognostic information. In patients with suspected left ventricular dysfunction, additional testing such as a fluid or exercise challenge may be helpful during right heart catheterisation to elicit occult post-capillary pulmonary hypertension, but these procedures should only be performed in experienced centres.

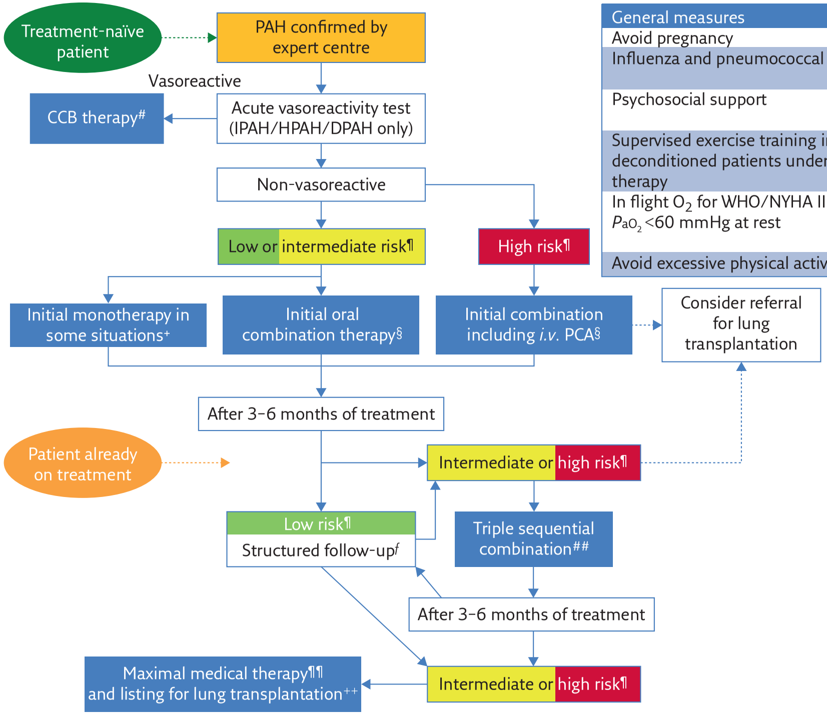
Treatment

The treatment algorithm for PAH is shown in figure 3, which is based on recommendations from the Sixth World Symposium on Pulmonary Hypertension and the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines. The different treatments have been evaluated by randomised control trials primarily in idiopathic PAH, heritable PAH, PAH due to anorexigen drugs and in PAH associated with connective tissue diseases or with congenital heart diseases (surgically corrected or not). Importantly, this treatment algorithm does not apply to groups 2, 3, 4 or 5 pulmonary hypertension.

General measures consist of providing psychosocial support and counselling, given the progressive nature of the disease, as well as preventative interventions like vaccinations and referral to an expert centre. Because of the high risk of morbidity and mortality associated with pregnancy in female patients, contraception and avoidance of pregnancy are recommended. Patients with resting hypoxaemia should be given continuous oxygen. Patients with a new diagnosis of PAH should be referred to an expert centre.

The initial treatment decision for newly diagnosed PAH patients depends on the results of acute vasoreactivity testing using inhaled nitric oxide or *i.v.* prostacyclin during a diagnostic right heart catheterisation. High doses of CCBs (*i.e.* nifedipine) can be used for patients with an acute vasoreactive response and who have idiopathic, heritable or drug-induced PAH. Long-term response to CCBs is rare in other types of PAH. Patients who are treated with high dose CCBs should be followed up in 3–4 months to confirm adequate clinical and haemodynamic improvement. For patients without acute vasoreactivity, a comprehensive and multidimensional risk assessment guides therapeutic choices (table 2). Oral PAH therapies such as an endothelin receptor antagonist (ERA) (*i.e.* bosentan, macitentan), a phosphodiesterase type-5 inhibitor (PDE5i) (*i.e.* sildenafil, tadalafil), a soluble guanylate cyclase inhibitor (*i.e.* riociguat) or an oral prostacyclin IP receptor agonist (*i.e.* selexipag) are usually used in combination or as single therapy in certain situations. PDE5i and riociguat both act through the nitric oxide signalling pathway and may not be used together. The AMBITION study was a prospective randomised controlled trial demonstrating that initial oral combination therapy with ambrisentan and tadalafil was more effective than either drug used as monotherapy in treatment-naïve patients with NYHA II–III symptoms; therefore, this (an ERA plus PDE5i) strategy is most frequently used. The quality of evidence for other combinations is less robust. For existing patients who are already on treatment and have not achieved a low-risk profile, sequential combination therapy can be considered. As there are no head-to-head studies comparing oral PAH therapies, the choice of initial therapy should take into account disease severity and a comprehensive risk assessment, side-effects, patient preferences and treating physician experience. For high-risk patients and those with signs of right ventricular failure, triple combination therapy including an ERA, PDE5i and an *i.v.* prostacyclin (*i.e.* epoprostenol, treprostinil) should be considered. *i.v.* epoprostenol remains the only therapy with a proven survival benefit in PAH and it may be used in combination with an ERA and a PDE5i or riociguat.

For all patients on PAH therapy, frequent reassessment is necessary with periodic risk assessment (table 2 and figure 3), as the response to initial therapy is a better predictor of future outcome than baseline haemodynamics or other risk parameters.


Treatment-naïve patient
PAH confirmed by expert centre
Vasoreactive
CCB therapy#
Acute vasoreactivity test (IPAH/HPAH/DPAH only)
Non-vasoreactive
Low or intermediate risk¶
High risk¶
Initial monotherapy in some situations+
Initial oral combination therapy§
Initial combination including i.v. PCA§
Consider referral for lung transplantation
After 3–6 months of treatment
Patient already on treatment
Intermediate or high risk¶
Low risk¶
Structured follow-upf
Triple sequential combination##
After 3–6 months of treatment
Maximal medical therapy¶¶ and listing for lung transplantation++
Intermediate or high risk¶

General measures	Supportive measures
Avoid pregnancy	Diuretics for RV failure/fluid retention
Influenza and pneumococcal vaccine	Continuous O_2 when P_{aO_2} consistently <60 mmHg
Psychosocial support	Oral anticoagulation for IPAH/HPAH/DPAH due to anorexigens
Supervised exercise training in deconditioned patients under medical therapy	Correction of anaemia and/or iron status
In flight O_2 for WHO/NYHA III/IV and P_{aO_2} <60 mmHg at rest	Avoid ACEI, ARBs, β-blockers and ivadrabine unless required by comorbid diseases
Avoid excessive physical activity	

Figure 3. Treatment algorithm for PAH. HPAH: heritable PAH; DPAH: drug-induced PAH; PCA: prostacyclin analogue; RV: right ventricle; WHO World Health Organization; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin-2 receptor antagonists. #*: 2015 ESC/ERS PH guidelines table 18;* ¶*: 2015 ESC/ERS PH guidelines table 13;* +*: 2015 ESC/ERS PH guidelines table 19;* §*: 2015 ESC/ERS PH guidelines table 20;* f*: 2015 ESC/ERS PH guidelines table 14;* ##*: 2015 ESC/ERS PH guidelines table 21;* ¶¶*: maximal medical therapy is considered triple combination therapy including* s.c. *or* i.v. *PCA (*i.v. *is preferred in high-risk status);* ++*: 2015 ESC/ERS PH guidelines table 22. Reproduced and modified from Galié* et al. *(2019).*

Additional therapies may be considered for patients who remain with intermediate or high-risk features after treatment initiation or changes. If a patient worsens, or still has an inadequate clinical response despite maximal therapy, lung transplantation should be considered. Atrial septostomy and palliative care are also considerations for end-stage patients who decline or are unable to receive lung transplantation due to contraindications or lack of availability.

Patients with CTEPH should be assessed by a multidisciplinary team of surgeons, radiologists and physicians to determine operability. For individuals with operable disease, PEA in an experienced surgical centre is the treatment of choice. PEA involves a sternotomy, cardiopulmonary bypass and deep hypothermia with full circulatory arrest while the occlusive material is dissected with the inner layer of the pulmonary arteries. In experienced surgical centres, PEA is associated with an in-hospital mortality of less than 2.5–5% and has the potential to improve symptoms, pulmonary haemodynamics, right ventricular function and survival. For patients with inoperable disease due to distal lesions or medical comorbidities, riociguat is currently the only approved PAH medical therapy. The randomised MERIT-1 study also showed improvements with macitentan, an ERA; however, this has not yet been approved by European or North American regulatory agencies. However, balloon pulmonary angioplasty is an emerging technique involving the dilation of multiple chronically obstructed pulmonary arteries, which can improve haemodynamics, symptoms and exercise capacity for inoperable patients.

Further reading

- Boucly A, *et al.* (2017). Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J*; 50: 1700889.
- D'Alonzo GE, *et al.* (1991). Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Int Med*; 115: 343–349.
- Delcroix M, *et al.* (2016). Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *Circulation*; 133: 859–871.
- Frost A, *et al.* (2019). Diagnosis of pulmonary hypertension. *Eur Respir J*; 53: 1801904.
- Galié N, *et al.* (2015). Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med*; 373: 834–844.
- Galié N, *et al.* (2015). 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*; 46: 903–975.
- Galié N, *et al.* (2019). Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J*; 53: 1801889.
- Humbert M, *et al.* (2019). Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *Eur Respir J*; 53: 1801887.
- Kim NH, *et al.* (2019). Chronic thromboembolic pulmonary hypertension. *Eur Respir J*; 53: 1801915.
- Simonneau G, *et al.* (2019). Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*; 53: 1801913.
- Weatherald J, *et al.* (2018). Prognostic value of follow-up hemodynamic variables after initial management in pulmonary arterial hypertension. *Circulation*; 137: 693–704.

Pulmonary vasculitis

George A. Margaritopoulos and Athol U. Wells

The principles of diagnosis and management are broadly similar across the individual pulmonary vasculitides, subdivided into primary systemic and secondary disorders (table 1). The main challenges for the clinician are:

- to recognise that vasculitis is a possible diagnosis;
- to make the diagnosis in nonclassical disease;
- to select a level of treatment appropriate to disease severity.

Granulomatosis with polyangiitis (GPA), eosinophilic granulamatosis with polyangiitis (EGPA) (the entity formerly known as Churg–Strauss syndrome) and microscopic polyangiitis (MPA) are the most frequent examples of anti-neutrophil cytoplasmic antibody vasculitides.

Epidemiology and pathogenesis

GPA is the third most prevalent systemic vasculitis (after giant cell arteritis and vasculitides in rheumatoid arthritis), with an annual incidence of 3–11 per million, largely affecting adults aged 30–50 years. EGPA has an annual incidence of 2.5–10 per million and mainly affects adults aged 30–50 years. In neither disorder is there a strong sex predilection. MPA has an annual incidence of 0.5–3.7 per million.

Anti-neutrophil cytoplasmic antibodies (ANCAs) are often present in systemic vasculitides involving the small and medium-sized vessels, including EGPA, GPA and MPA. ANCAs are subcategorised as cytoplasmic, perinuclear or atypical, and are directed primarily against proteinase-3 in GPA (cytoplasmic) and against myeloperoxidase (MPO) in EGPA (perinuclear). However, all ANCA patterns have been reported in both disorders. *In vitro* and animal data suggest that ANCAs interact with primed neutrophils, leading to endothelial damage and further neutrophil recruitment. Both diseases are generally considered to be triggered by foreign agents, including

Key points

- Haemoptysis is often scant or absent in diffuse alveolar haemorrhage.
- Vasculitis must often be treated empirically, in the absence of full diagnostic clinical criteria or a histological diagnosis.
- Initial treatment should be definitive, even when the diagnosis is tentative.
- Chronic infection and malignancy are the most frequent differential diagnosis.

Table 1. Classification of pulmonary vasculitis

Vasculitis	Frequency of lung involvement
Primary[#]	
Large vessel	
Giant-cell arteritis	Rare
Takayasu's arteritis	Frequent
Medium-sized vessel	
Polyarteritis nodosa	Rare
Kawasaki disease	No
Small vessel[¶]	
GPA	Frequent
EGPA	Frequent
MPA	Frequent
Henoch–Schönlein purpura	No
Essential cryoglobulinaemia	No
Secondary	
Rheumatological	
Pulmonary–renal (*e.g.* Goodpasture's syndrome)	
Relapsing polychronditis	
Behçet's syndrome	
Chronic infection	
Lymphoma	
Drugs	

[#]: 2012 revised Chapel Hill international consensus nomenclature; [¶]: with variable medium-sized vessel involvement.

drugs and infections, with the most suggestive data relating to chronic nasal carriage of *Staphylococcus aureus* in GPA.

Clinical presentation

Vasculitis should be suspected in diffuse alveolar haemorrhage. Haemoptysis is often absent or scant. Diffuse alveolar haemorrhage should be suspected when unexplained infiltrates on chest imaging are associated with a fall in haemoglobin over a day or two or, in chronic low-grade haemorrhage, with an iron-deficiency anaemia. Bronchoalveolar lavage is usually diagnostic of haemorrhage. Vasculitis should also be suspected in:

- patients presenting with breathlessness on exertion and an unexplained isolated or disproportionate reduction in T_{LCO};
- patients with features of an underlying systemic vasculitis, such as GPA, EGPA or a pulmonary–renal syndrome (of which Goodpasture's disease is the best known example).

Investigations that tend to be useful in suspected vasculitis are shown in table 2.

Eosinophilic granulamatosis with polyangiitis

The American College of Rheumatology definition of EGPA requires the satisfaction of at least four out of six criteria (table 3). Typically, there is a prodrome of rhinitis with nasal polyps and the eventual development of late-onset asthma, followed by eosinophilia

Table 2. Useful investigations for suspected pulmonary vasculitis

Imaging
Chest radiography
HRCT
Lung function tests
Pulmonary function tests ($T_{\mathrm{LCO}}/K_{\mathrm{CO}}$)
Arterial gases (wide A–a gradient)
Renal function
Urine dipstick testing and microscopy for proteinuria, haematuria and cellular casts
Estimation of renal function
Consider renal biopsy (if evidence of nephritis)
Immunology
ANCAs
Anti-GBM antibodies
Immune complexes
CTD-related antibodies (ANA, ENA, anti-CCP, antiphospholipid antibodies and lupus anticoagulant)
Bronchoscopy/bronchoalveolar lavage
Iron-laden macrophages (in alveolar haemorrhage)
Eosinophilia (in EGPA)
Exclusion of low respiratory tract infections
Assessment of the large airways (stenosis-endobronchial lesion)
Biopsy
Renal
Skin
Lung (surgical)

GBM: glomerular basement membrane; ANA: antinuclear antibody; ENA: extractable nuclear antibody; anti-CCP: anti-cyclic citrullinated peptide antibody.

in tissue or peripheral blood and, ultimately, systemic vasculitis. Involvement of the lung parenchyma occurs in up to two-thirds of EGPA patients. Other frequent sites of involvement include the nervous system (especially mononeuritis multiplex) in 75%, skin (60%), joints and, less frequently, the kidneys and gastrointestinal tract. Importantly, symptomatic cardiac involvement occurs in 27–47% of EGPA cases, represents the major cause of early death and is associated with poor long-term prognosis. Although endomyocardial infiltration is the dominant condition, arrhythmia, pericarditis and valvular defects may also occur. When cardiac involvement is suspected, the performance of echocardiogram, cardiac MRI and positron emission tomography should be considered. Pulmonary infiltrates are seen in 80% of patients. The most frequent findings on HRCT are patchy ground-glass infiltration and patchy

Table 3. American College of Rheumatology diagnostic criteria for EGPA (four out of six required)

Presence of asthma
Peripheral blood eosinophilia (>10%)
Evidence of a neuropathy in a vasculitic pattern (*e.g.* mononeuritis multiplex)
Transient pulmonary infiltrates
A history of sinus disease
Evidence of extravascular eosinophilia on biopsy

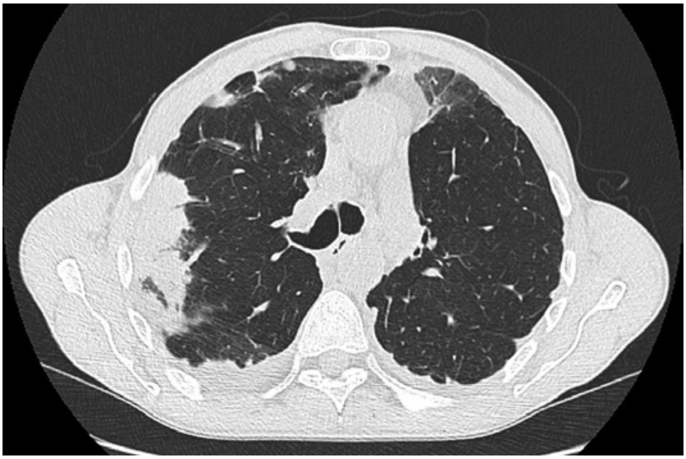


Figure 1. High-resolution CT showing peripheral consolidations and patchy ground-glass infiltration.

consolidation (figure 1). An extensive ground-glass appearance is usual in patients which alveolar haemorrhage due to capillaritis, whereas consolidation is more suggestive of granuloma formation in association with involvement of medium-sized vessels. Pulmonary infiltrates are much more common than pulmonary nodules and, in contrast to GPA, cavitation of nodules is extremely rare. Pleural disease is present in 50%. The classical triad at lung biopsy is necrotising angiitis, granulomata and tissue eosinophilia. The diagnostic role of ANCA, tested with indirect immunofluorescence and ELISA, continues to be debated. ANCAs, usually perinuclear, are present in up to two-thirds of patients, but also occur in many other non-vasculitic autoimmune and infectious conditions. In the clinical context of asthma and eosinophilia, anti-MPO ANCA positivity is highly suggestive of EGPA but, conversely, ANCA negativity does not rule out the diagnosis.

Granulomatosis with polyangiitis

The classic historical GPA triad consisted of renal, lower respiratory tract and upper respiratory tract involvement. Most often, chronic rhinitis, sinusitis or mastoiditis progresses to generalised disease over months to years, with lower respiratory tract involvement in 65–85%, including diffuse alveolar haemorrhage, which may be life-threatening and tends to occur before specific pulmonary manifestations of GPA are apparent. Fever and weight loss are frequent. There is a wide range of extrapulmonary organ involvement. Lung involvement is asymptomatic in one-third of cases. Chest imaging may show cavitary or non-cavitary nodules, localised or diffuse infiltrates (which may represent alveolar haemorrhage), or evidence of large and small airway disease (figure 2). The cardinal histological features are granulomatous inflammation and necrotising vasculitis, affecting small to medium-sized vessels (figure 3). In advanced pulmonary disease the hazards of biopsy should prompt a search for an alternative biopsy site, including the kidney, skin and skeletal muscles. Endoscopic nasal biopsy appearances are most often nonspecific, although positive features in a few cases provide a definitive diagnosis. As in EGPA, the diagnosis does not require ANCA positivity; cytoplasmic ANCAs are not present in all cases (especially when GPA is confined to the lungs), and are also found in other vasculitides, chronic bacterial infections and cryoglobulinaemia.

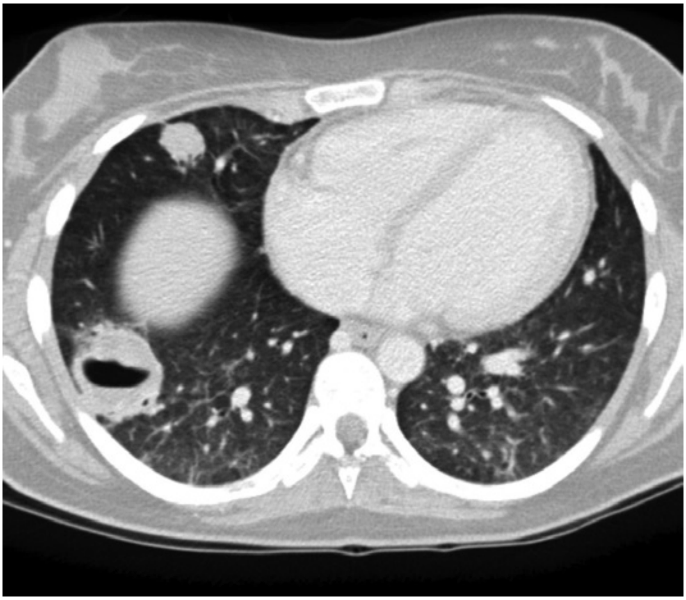


Figure 2. CT showing cavitary or non-cavitary nodules.

Microscopic polyangiitis

Among vasculitides, MPA, a necrotising vasculitis affecting small to medium-sized vessels, is the main clinical mimic of GPA. Although pulmonary involvement is less frequent than in GPA, this disorder also often presents with diffuse alveolar haemorrhage, which can have a poor prognosis. Necrotising glomerulonephritis, mononeuritis multiplex and skin lesions are variably present. The cardinal histological distinction is the absence of granulomas, which are characteristically present in GPA. Microscopic polyangiitis also needs to be distinguished from polyarteritis nodosa

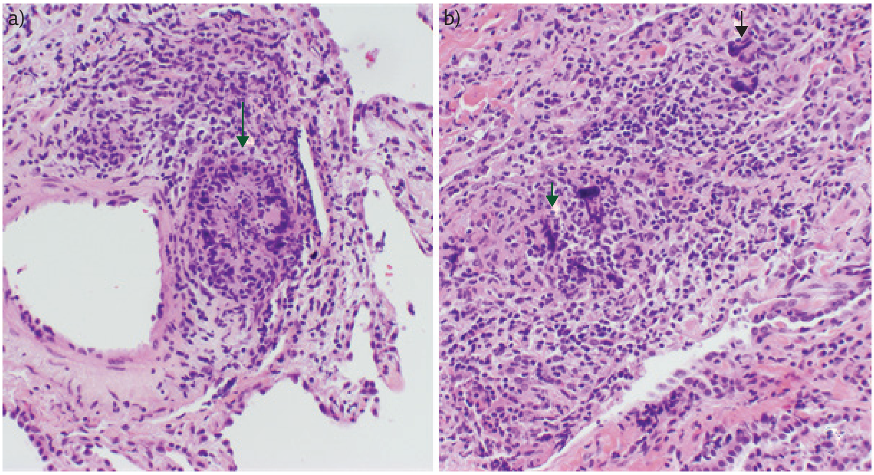


Figure 3. a) Neutrophilic microabscess with central necrosis surrounded with multinucleated giant cells by a vascular wall and b) abundant multinucleated giant cells within a background of acute lung injury. Case courtesy of A. Montero-Fernadez, Manchester University Hospital, Manchester, UK.

that, by definition, only affects arteries, rarely arterioles and never small vessels. Pulmonary fibrosis is a rare manifestation of vasculitis. It is more common in MPA and is characterised most frequently by the presence of the pattern of usual interstitial pneumonia on HRCT and by the presence of ANCA-MPO antibodies.

Diagnosis of vasculitis

A confident diagnosis requires histological confirmation or satisfaction of the requisite number of clinical criteria. However, many patients with vasculitis have features overlapping between diagnostic entities with transient or non-fulfilment of diagnostic criteria. Thus, a versatile diagnostic approach is required. When vasculitis is suspected but full clinical criteria are not satisfied, a histological diagnosis should be made, if possible. However, a negative biopsy does not exclude vasculitis, which may be patchy or give rise to nonspecific inflammatory change (as in upper airway biopsies in GPA patients).

Thus, the diagnosis of a vasculitic syndrome is sometimes necessarily empirical, with chronic infection and malignancy the most frequent differential diagnoses. In such cases, initial treatment and monitoring should be as for the vasculitic syndrome most closely corresponding to the clinical presentation in that patient. Initial treatment should be definitive as a clear response provides important support for the diagnosis, whereas a tentative therapeutic approach often prolongs diagnostic uncertainty.

Prognosis

The poor historical outcome of the vasculitic syndromes has been transformed by more aggressive therapy but also by the increasing detection of milder disease, including patients with limited involvement. In localised pulmonary GPA and EGPA alike, the outcome is much better than with multiorgan involvement. In EGPA, the prognosis worsens strikingly with two or more extrapulmonary complications (5-year survival 54%). Mortality is largely ascribable to sepsis (as a complication of treatment) or disease progression. In, GPA, mortality from progressive disease is most commonly due to renal failure or lung involvement. By contrast, in EGPA, cardiac disease is the leading cause of death, with mortality also ascribable to renal failure, cerebrovascular involvement, gastrointestinal disease or lung disease (10% of deaths). In EGPA, ANCA may hold a prognostic significance. ANCA-positive patients are more likely to have a 'vasculitic' phenotype with glomerulonephritis, mononeuritis multiplex and relapses. In ANCA-negative patients the prognosis is poorer, mainly because of the higher frequency of cardiomyopathy despite a lower likelihood of relapse.

Treatment

Remission and induction therapy of ANCA-associated vasculitides should be dictated by disease extent and severity. Newly diagnosed ANCA-associated vasculitides can be subdivided into 1) relatively benign disease (i.e. non-organ threatening); 2) potentially dangerous disease involving major organs; and 3) life-threatening disease, most often rapidly progressive renal failure, pulmonary haemorrhage or severe cardiac involvement in EGPA.

The management is commonly divided into two phases: 1) an induction phase, in which an aggressive approach is used to induce remission; and 2) a maintenance phase in which therapy is deescalated to minimise adverse side effects whilst maintaining remission.

Induction phase

The induction phase is described in table 4.

Table 4. Induction phase

Severity	Recommendation
Relatively benign disease	Glucocorticoids in combination with either methotrexate or mycophenolate mofetil
Potentially dangerous disease involving major organs	Glucocorticoids in combination with either cyclophosphamide or rituximab
Life-threatening disease (diffuse alveolar haemorrhage, rapidly progressive glomerulonephritis)	As above; additionally consider plasma exchange, dialysis and ECMO (in severe cardiac and lung disease)

ECMO: extracorporeal membrane oxygenation.

Glucocorticoid regimens

The initial dose of oral steroids is 1 mg·kg·day^{-1} but in more severe cases intravenous administration at the dose of 7.5–15 mg·kg·day^{-1} for 1–3 consecutive days is preferred in order to achieve a quicker response. Subsequently, oral steroids can be introduced at a lower dose, avoiding as much as possible the long-term steroid-related side effects such as infections, diabetes and osteoporosis.

Cyclophospamide

Clinical trials and long-term follow-up data showed that pulsed cyclophosphamide regimens (15 mg·kg^{-1} every 2–3 weeks) are favoured over the oral ones due to the reduced total dose of cyclophosphamide overall and reduced risk of bladder-related complications despite a slightly higher relapse rate.

Rituximab

Rituximab, at the dose of 375 mg·m^{-2} of body surface area once a week for four infusions, was non inferior to cyclophosphamide and appeared more effective for relapsing disease. Rituximab may be preferable to cyclophosphamide in patients who wish to preserve their reproductive potential. Cyclophosphamide is associated with reduced ovarian reserve, ovarian failure and male infertility.

Maintenance phase

For remission maintenance of antibody vasculitide, treatment with low-dose glucocorticoids in combination of second-line agents is recommended. Azathioprine at the dose of 2 mg·kg·day^{-1} is slightly preferred in GPA and EGPA. Methotrexate (20–25 mg·week^{-1}), rituximab at a fixed dose of 500 mg and mycophenolate mofetil have also been proved efficacious in this regard.

Major relapse of organ threatening or life threatening disease

Treatment as per new disease, with glucocorticoids in combination with either cyclophosphamide or rituximab, is recommended. The use of rituximab is preferred over cyclophosphamide due to drug's related toxicity. In non-severe relapses in antibody vasculitides, a temporary increase in the glucocorticoid dose could help to achieve disease remission although relapses in short time could be observed.

Refractory disease

In refractory disease, a careful re-evaluation is required with regards to the accuracy of the initial diagnosis, the use of the optimal doses of the medications, the activity of the disease and finally the presence of infection, malignancy and other comorbidities. A switch from cyclophosphamide to rituximab or from rituximab to cyclophosphamide and a referral to expert centre is strongly recommended. Intravenous immunoglobulins can be considered as additional therapy for patients on glucocorticoids (and/or other immunosuppressants) with refractory disease or with drug-induced hypogammaglobulinemia and severe and/or recurrent infections.

Localised upper airway disease

In limited isolated upper airways disease there are limited data supporting the use of oral steroids as monotherapy and/or a single cytotoxic agent such as methotrexate, azathioprine and mycophenolate mofetil. In GPA, co-trimoxazole therapy has been efficacious in localized respiratory tract disease and may have an ancillary role in maintaining remission.

Mepolizumab

Mepolizumab, a humanised monoclonal IgG1 antibody that binds free IL-5 which is the major specific factor for eosinophil growth, differentiation and survival, is the first biological agent approved to treat EGPA. A milestone trial showed that patients with relapsing or refractory EGPA treated with mepolizumab had clinically relevant improvements in the rates of protocol defined remission and relapse compared to placebo, which allowed for reduced glucocorticoid use. Remission was less likely for patients with baseline eosinophil counts <150 per mm^3. However, 47% of the treated patients did not have protocol-defined remission which raised the possibility of different sub-phenotypes in EGPA.

Antibiotics

As acute infection can fuel vasculitic activity, a policy of early broad-spectrum antibiotic therapy for acute infection appears logical. This approach requires patients to have a home supply of antibiotics and to initiate treatment at the first symptomatic management of an infection. In case of recurrent infection, the use of prophylactic antibiotics may be required to prevent the reactivation of vasculitis. Prophylactic co-trimoxazole (trimethoprim 160 mg/sulphamethoxazole 800 mg three times a week) is often used with prolonged intense immunosuppression (cyclophosphamide, rituximab), to reduce the risk of opportunistic *Pneumocystis jirovecii* infection.

Further reading

- Commarmond C, *et al.* (2014). Pulmonary fibrosis in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis: a series of 49 patients and review of the literature. *Medicine (Baltimore)*; 93: 340–349.
- Frankel SK, *et al.* (2012). The pulmonary vasculitides. *Am J Respir Crit Care Med*; 186: 216–224.
- Groh M, *et al.* (2015). Eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med*; 26: 545–553.
- Guillevin L, *et al.* (1996). Prognostic factors in polyarteritis nodosa and Churg–Strauss syndrome. A prospective study in 342 patients. *Medicine (Baltimore)*; 75: 17–28.
- Jennette JC, *et al.* (2013). 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. *Arthritis Rheum*; 65: 1–11.

- Kronbichler A, *et al.* (2018). Trimethoprim-sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis. *Ann Rheum Dis*; 77: 1440–1447.
- Lhote F, *et al.* (1998). Polyarteritis nodosa, microscopic polyangiitis and Churg–Strauss syndrome. *Semin Respir Crit Care Med*; 19: 27–46.
- Wechsler ME, *et al.* (2017). Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med*; 376: 1921–1932.
- Yates M, *et al.* (2016). EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis*; 75: 1583–1594.

Arteriovenous malformations

Camilla Poggi, Sara Mantovani, Daniele Diso, Jacopo Vannucci,
Federico Venuta and Marco Anile

Pulmonary arteriovenous malformations (PAVMs) are abnormal communications between the pulmonary arteries and pulmonary veins bypassing the normal capillary bed and providing an intrapulmonary right-to-left shunt. Signs and symptoms are related to the degree of shunt, and the size and number of lesions. The majority of PAVMs are associated with hereditary haemorrhagic telangiectasia (HHT); more rarely, they can evolve after gestational trophoblastic disease, trauma, infections (actinomycosis or schistosomiasis), hepatic cirrhosis related to hepatopulmonary syndrome or after surgical repair of cyanotic heart defects generating a cavopulmonary shunt. Churton described the first case in the 1897 during an autopsy of a 12-year-old patient with epistaxis, haemoptysis and pulmonary systolic bruit. Although they have usually been considered rare entities, with an incidence of three cases per 100 000, in the last decade, a prevalence of one case in every 2000 CT scans has been reported. This examination certainly allows higher accuracy in asymptomatic patients. The most frequent age of presentation is the third decade; however, it is also possible to detect them at other ages.

Aetiology

~90% of patients with PAVMs are affected by HHT or Rendu–Osler–Weber disease. HHT is an autosomal dominant disorder characterised by vascular anomalies involving several organs; the clinical presentation includes recurrent epistaxis, mucocutaneous telangiectasia and arteriovenous malformations. HHT is diagnosed using the Curaçao criteria (table 1). Two more frequent types of HHT due to different mutations are recognised and show different phenotypes: HHT1 is related to a mutation of the *ENG* gene encoding endoglin; it shows a higher prevalence of PAVMs and cerebral malformations. HHT2 is caused by a mutation in *ACVLR1* encoding activin receptor-like kinase; it shows a higher incidence of pulmonary hypertension and hepatic arteriovenous malformations. Due to the fact that the prevalence of HHT is age related, the manifestations of this disease may increase with ageing, becoming completely evident during the third decade of life. More frequently, bilateral and

Key points

- Pulmonary arteriovenous malformations (PAVMs) are strongly associated with hereditary hemorrhagic telangiectasia.
- PAVMs are more frequent in the lower lobes.
- The development of PAVMs is age related.
- Embolisation is the gold standard treatment.

Table 1. Curaçao criteria for HHT

Epistaxis
Telangiectasia
Visceral lesions
Family history
When three criteria are present: definite HHT; when two criteria are present: suspicion of HHT; when one criterion is present: HHT is unlikely.

multiple localisations are detected in HHT-related cases. Sporadic forms due to infections, traumas or iatrogenic pulmonary shunts often appear as isolated nodules.

Pathophysiology

Based on number, location and morphology, PAVMs can be classified as single or multiple, unilateral or bilateral, and simple or complex; because of the increased blood flow and pressure in the inferior part of the lung, lower lobes are most frequently affected. A single feeding artery, an aneurysmal sac and an efferent vein define PAVMs as simple. The artery is usually a branch of the pulmonary artery; however, in rare cases, a systemic artery (bronchial or intercostal) could be involved. The aneurysmal sac often drains into a branch of a pulmonary vein, although communications with the inferior vena cava and left atrium have been reported. In cases of complex PAVMs, there are multiple feeding arteries.

The mutations involved with the development of PAVMs cause an imbalance between the levels of proangiogenic vascular endothelial growth factor and antiangiogenic transforming growth factor-β; as a result, the wall of the aneurysmal sac is thin and fragile with an increased risk of rupture and intrapulmonary bleeding. The size of PAVMs increases progressively with age. Radiologically, they usually start with a ground-glass opacity (GGO) due to the enlargement of postcapillary venules and an inflammatory response. Later, small vessels with aberrant connections between arteries and venules can be detected within the GGO. With time, after the enlargement of the efferent vein, the typical presentation of PAVMs is radiologically visible.

Clinical presentation

PAVMs can be completely asymptomatic or show a number of symptoms related to the size, location, flow through the malformation, degree of intrapulmonary shunt and association with HHT. Dyspnoea, hypoxaemia at rest or on exertion, and cyanosis are the most frequent symptoms; since the prevalence of PAVMs is higher in the lower lobes, orthodeoxia (worsening of hypoxaemia in the upright position) and platypnoea (worsening of dyspnoea in the upright position) may be present. Neurological manifestations, such as cerebral abscesses, ischaemic strokes and migraine headaches, are due to the paradoxical embolisation related to right-to-left shunt; a strong association between a diameter of the feeding artery >3 mm and neurological symptoms has been reported. Frailty of the endothelial layer caused by a deficiency of connective tissue may lead to haemoptysis, haemothorax and intrapulmonary haemorrhage; these life-threating complications are more frequent during pregnancy, with an increased risk of maternal death.

Diagnosis

Physical examination, chest radiography and evaluation of gas exchange are mandatory in patients with suspected HHT. In cases of high suspicion of PAVMs, the screening test of choice is transthoracic contrast echocardiography (TTCE). TTCE assess the

Table 2. Grading of TTCE

Grade 0	No bubbles
Grade 1	<20 bubbles
Grade 2	Moderate filling
Grade 3	Complete filling

presence of right-to-left pulmonary shunt by visualising air microbubbles in the left side of the heart (following injection of shaken saline) after three or four cardiac cycles. A grading based on the amount of visualised bubbles has been proposed to measure the severity of shunt (table 2). A positive TTCE screening must be confirmed by CT pulmonary angiography, possibly with three-dimensional reconstructions. Recently, MRI has gained a role in the detection and pretreatment assessment of PAVMs due to the possibility of avoiding radiation and iodinate contrast; in addition, it has been suggested that MRI could improve screening due to its sensitivity for identifying lesions 2 mm in diameter. Other more invasive diagnostic tools including catheter-direct angiography, cardiac catheterisation and lung perfusion scan are considered optional when borderline or unclear manifestations are present.

Treatment

Until 1978, surgery, including the complete spectrum of pulmonary resections, was considered the gold standard. More recently, the advent of techniques for arterial embolisation allowed successful treatment of PAVMs less invasively. Now, according to international guidelines, surgery is considered only in life-threatening situations due to massive bleeding and in centres without the availability of radiologists familiar with the techniques of embolisation. The basic principle of this technique is to occlude the feeding artery, or arteries, very close to the fistulous communication including all the feeding arteries, sparing as much pulmonary parenchyma as possible. Up to four PAVMs can be treated in a single step; in cases where more arteries need to be embolised, multiple treatments are required. Several embolic materials have been employed, including coils, balloons and vascular plugs; the choice of the most appropriate device is related to the type and size of PAVM, and the operator's preference. Successful occlusion improves oxygenation, and decreases dyspnoea at rest and fatigue on exertion; furthermore, it reduces the risk of pulmonary haemorrhage and paradoxical embolisation. Recanalisation of the feeding artery could be due to a size mismatch between the materials employed and PAVM diameter; other prognostic factors may be pulmonary hypertension and presence of hepatic arteriovenous fistulas at the time of diagnosis. In order to reduce the incidence of recanalisation, the simultaneous use of different devices could be useful. Follow-up is planned with CT scanning at 6 and 12 months, and subsequently, every 3 years.

Further reading

- Cartin-Ceba R, *et al.* (2013). Pulmonary arteriovenous malformations. *Chest*; 144: 1033–1044.
- Saboo SS, *et al.* (2018). Pulmonary arteriovenous malformations: diagnosis. *Cardiovasc Diagn Ther*; 8: 325–337.
- Shovlin CL (2014). Pulmonary arteriovenous malformations. *Am J Respir Crit Care Med*; 190: 1217–1228.
- Tellapuri S, *et al.* (2018). Pulmonary arteriovenous malformations. *Int J Cardiovasc Imaging*; https://doi.org/10.1007/s10554-018-1479-x.

Chest wall disorders

Pierre-Emmanuel Falcoz, Nicola Santelmo, Anne Olland
and Gilbert Massard

There is a large and diverse group of congenital abnormalities of the thorax that manifest as deformities and/or defects of the anterior chest wall. Depending on the severity of the case, there may be cardiopulmonary (tolerance to exercise) or psychological implications.

This diverse group includes:

- pectus excavatum or ‘funnel chest’
- pectus carinatum or ‘keel chest’
- Poland syndrome
- cleft sternum

Among these, pectus excavatum and pectus carinatum are the two most common chest wall abnormalities.

Pathogenesis

Over the years, the theories concerning the pathogenesis of pectoral deformities evolved from substernal ligament traction to overgrowth of the rib cartilage and later to a stress–strain imbalance. The genetic aspects of pectus deformities have just started to emerge and, hopefully, will answer many questions.

Key points

- The two most common chest wall abnormalities are pectus excavatum and pectus carinatum.
- The most common surgical procedures for pectus excavatum repair are the modified Ravitch technique (major deformation) and the Nuss procedure (minor deformation). The Rudakov approach is a very promising and innovative technique with the implantation of an elastic and thermomodulable Nitinol bar.
- Careful pre-operative evaluation on the basis of clinical and psychological symptoms is required to select potential candidates for surgical remodelling.
- The optimal timing of surgical repair would be after the main growth has stopped (late teens or early 20s).

Pectus excavatum

Pectus excavatum is a recessively inherited chest wall deformity with an occurrence of 0.3% of all births (9:1 predominance in males). In patients with pectus excavatum, the normally moderately convex contour of the anterior chest wall is replaced by precordial depression. Depending on the severity of the anomaly, the sternovertebral space is narrowed, there is a shift of the heart into the left hemithorax and pulmonary expansion is confined.

The indications for surgery may be summarised as follows.

- Aesthetic (psychological repercussion)
- Symptom
- Exercise intolerance, decreased endurance or exercise-induced asthma
- Body images issues (CT scan)
- Pain
- Abnormal/low FVC, FEV$_1$ or maximum voluntary ventilation
- Decreased oxygen pulse, oxygen uptake or V'_E
- Echocardiogram: compression of right atrium/right ventricle (rare)
- CT Haller index >3.0
- Calliper measurement depth >2.5 cm

Pectus carinatum

In pectus carinatum, the clinical aspect includes a variety of protrusion deformities of the anterior chest wall. The most common variety consists of anterior displacement of the sternal gladiolus with the appropriate cartilages in tow. In severe forms, there is also a narrowing of the transverse diameter of the chest, which seems to further exaggerate the anomaly.

The indications for surgery may be summarised as follows.

- Aesthetic (psychological repercussion)
- Pain
- Frequent injury
- Body image issues
- Abnormal pulmonary function testing

Surgical treatment

Pectus excavatum

Although there are several different techniques used by surgeons, most repairs performed today will be undertaken either by the modified Ravitch technique (major deformation) or by a minimally invasive procedure (Nuss or Rudakov techniques) for less significant deformation.

The Ravitch technique requires the exposition of the thorax's anterior region (horizontal inframammary fold incision preferred) with resection of costal cartilages affected bilaterally, the performance of a cross-sternal osteotomy with the placing of a temporary stabiliser (support bar anterior to the sternum) and the development of a muscular flap.

The Nuss technique is an alternative and new technique performed by means of minimally invasive surgery, and based on the skeleton's malleability and the remodelling capacity of the thorax. The technique consists of the implantation of a retrosternal steel bar that modifies the concavity of the sternum while maintaining the contour of the reformed thorax, all by means of two small incisions on each side of the thorax. In terms of chest wall kinematics, the Nuss procedure increases chest wall volume by 11% without affecting chest wall displacement or rib cage configuration.

The Rudakov technique represents a double innovation. First, staged subperichondral resections of all deformed cartilages are performed through two short incisions in the submammary fold. Second, the sternum is lifted up and stabilised with an original Nitinol implant (KRI bar; KIMPF, Moscow, Russia). The shape of this implant mimics a seagull spreading its wings: the wing-parts lie down laterally onto the ribs and stabilisers may be added to neutralise rotational stress; the body part presents a slight depression hosting the sternum. Nitinol offers two fundamental properties: thermomodulation and elasticity with shape memory. The implant softens when cooled down and may be bent for easy insertion into a retrosternal tunnel created by blunt finger dissection; it pops back to its initially customised shape when heated above 27ºC. Elasticity with shape memory offers dynamic osteosynthesis with reduced pain.

Pectus carinatum

The repair of pectus carinatum, including exposure, detachment of the pectoralis muscles, transverse osteotomy and resection of the deformed cartilages, is largely identical to that described in pectus excavatum. Operative correction requires double bilateral chondrotomy parasternally and at points of transition to the normal ribs, followed by detorsion of the sternum, retrosternal mobilisation and correction of the everted sternum, as well as of the everted and inverted ribs. After incomplete wedge osteotomy, the mobilised sternum is finally stabilised by a temporary support bar anterior to the sternum and cartilages (in place for ≥6 months).

Controversies

Some controversies do need to be mentioned. First, concerning pectus excavatum, there has never been a randomised controlled trial comparing the results of the two most common surgical procedures. The meta-analysis by Nasr *et al.* (2010) comparing the Nuss procedure and the Ravitch technique repair suggested no differences with respect to overall complications, length of hospital stay or time to ambulation. Secondly, concerning the optimal timing of surgical repair, it seems that the best time for repair would be after the main growth has stopped (*i.e.* after adolescence in the late teens or early 20s) as opposed to early repair. Although the operation is more traumatic after adolescence, the results are far better with minimal recurrence. Thirdly, the goal of such an approach remains elusive. Not only are we unable to reach an agreement on such simple issues as how to measure the clinical or even the anatomical severity of pectoral deformities, but we are still engaged in a seemingly endless debate with the insurance companies as to whether these often physiologically and psychologically crippling abnormalities should be even considered a 'disease' at all.

Conclusion

Chest wall abnormalities (pectus excavatum and pectus carinatum) are a relatively rare problem but are commonly seen in the practice of general thoracic surgery.

Careful pre-operative evaluation based on clinical and psychological symptoms is required to select potential candidates for surgical remodelling. Surgical procedures, based on the surgeon's personal expertise, are currently relatively well codified and provide satisfactory results with a low rate of complications.

Further reading

- Binazzi B, *et al.* (2012). Effects of the Nuss procedure on chest wall kinematics in adolescents with pectus excavatum. *Respir Physiol Neurobiol*; 183: 122–127.
- Colombani PM (2009). Preoperative assessment of chest wall deformities. *Semin Thorac Cardiovasc Surg*; 21: 58–63.
- Emil S, *et al.* (2012). Pectus carinatum treatment in Canada: current practices. *J Pediatr Surg*; 47: 862–826.
- Feng J, *et al.* (2001). The biomechanical, morphologic, and histochemical properties of the costal cartilages in children with pectus excavatum. *J Pediatr Surg*; 36: 1770–1776.
- Fonkalsrud EW, *et al.* (2004). Less extensive techniques for repair of pectus carinatum: the undertreated chest deformity. *J Am Coll Surg*; 198: 898–905.
- Gurnett CA, *et al.* (2009). Genetic linkage localizes an adolescent idiopathic scoliosis and pectus excavatum gene to chromosome 18 q. *Spine*; 34: E94–E100.
- Haller JA, *et al.* (1989). Evolving management of pectus excavatum based on a single institutional experience of 664 patients. *Ann Surg*; 209: 578–583.
- Huddelston CB (2004). Pectus excavatum. *Semin Thorac Cardiovasc Surg*; 16: 225–232.
- Massard G, *et al.* (2017). Alternatives to titanium implants for pectus excavatum repair. *Ann Thorac Surg*; 104: 2121.
- Nasr A, *et al.* (2010). Comparison of the Nuss and the Ravitch procedure for pectus excavatum repair: a meta-analysis. *J Pediatr Surg*; 45: 880–886.
- Nuss D, *et al.* (1998). A ten-year review of minimally invasive technique for the correction of pectus excavatum. *J Pediatr Surg*; 33: 545–552.
- Ravitch MM (1949). The operative treatment of pectus excavatum. *Ann Surg*; 129: 429–444.
- Rudakov SS, *et al.* (2011). The radical minimal access thoracoplasty by funnel chest in adults. *Khirurgiia (Mosk)*; 7: 36–42.
- Robicsek F, *et al.* (2009). Surgical repair of anterior chest wall deformities: the past, the present, the future. Introduction. *Semin Thorac Cardiovasc Surg* 2009; 21: 43.
- Robiscek F, *et al.* (2009). Surgical repair of pectus excavatum and carinatum. *Semin Thorac Cardiovasc Surg*; 21: 64–75.
- Saxena AK, *et al.* (1999). Surgical repair of pectus carinatum. *Int Surg*; 84: 326–330.
- Shamberger SC, *et al.* (1995). Congenital deformities. *In*: Pearson FG, *et al.*, eds. *Thoracic Surgery*. New York, Churchill Livingstone; pp.1189–1209.
- Shu Q, *et al.* (2011). Experience in minimally invasive Nuss operation for 406 children with pectus excavatum. *World J Pediatr*; 7: 257–261.

Neuromuscular disorders and the diaphragm

Michael I. Polkey and Anita K. Simonds

Causes

The causes of respiratory muscle weakness can be tabulated in several ways (table 1), but for the clinician the most important distinction is likely to be the speed of onset of symptoms and whether or not the patient has a known underlying neurological disease.

Because respiratory muscle weakness is rare it should be considered in the differential diagnosis of patients who present with breathlessness or hypercapnic respiratory failure where the symptoms cannot be explained by radiographic appearances, body shape or habitus, or obstructive spirometry.

Respiratory failure is inevitable in some neurological conditions, for example Duchenne muscular dystrophy or spinal muscular atrophy, but in others it is only an occasional complication or, as for example in multiple sclerosis, depends on the site of involvement. In the conditions where respiratory failure is inevitable assessment of respiratory muscle function with expectant assessment of carbon dioxide retention is recommended, because it reduces the likelihood of unplanned respiratory crises. Respiratory complications can occur more generally in a number of neurological conditions *via* the mechanisms of aspiration or recurrent chest infections.

Among patients presenting with unexplained and isolated respiratory muscle weakness three conditions should be carefully considered. Neuralgic amyotrophy is a sudden onset brachial neuritis. Respiratory muscle weakness is often preceded by chest pain, which can be sufficiently severe to trigger cardiac investigation, and breathlessness may follow a few days later. Pain may be felt in the ‘badge area’ of the thorax and at the tip of the scapula. There may be associated upper limb weakness and consequent signs. Isolated respiratory muscle weakness is the presenting feature in just 3% of patients with motor neurone disease/amyotrophic lateral sclerosis (ALS), and these patients typically present with a 1–3 month history of breathlessness

Key points

- Respiratory muscle weakness should be considered in patients with breathlessness and/or ventilatory failure when the cause cannot be explained by radiological findings, body shape or habitus, or obstructive spirometry.
- A normal supine vital capacity measurement generally excludes respiratory muscle weakness.
- Bedside tests of pressure measured at the mouth or nose can be used as a screening test, but require voluntary effort.

Table 1. Causes of respiratory muscle weakness

By pathology		
Nerve	**Neuromuscular junction**	**Muscle**
ALS	Myasthenic syndromes	Muscular dystrophies
Guillain–Barré syndrome	Botulism	ICUAW
ICUAW	Lambert–Eaton syndrome	Pompe's disease
Envenomation	Poisoning (nerve agents)	Hypokalaemia/other biochemical
Polio		
By speed of onset		
Rapid onset (hours/days)	Envenomation Guillain–Barré syndrome Myasthenic decompensation Hypokalaemia/other biochemical Acute polio Poisoning (nerve agents) Organophosphates ICUAW	
Slow onset (months/years)	Past-polio syndrome Muscular dystrophies ALS Pompe's disease	

ICUAW: intensive care unit-acquired weakness. Reproduced from Polkey (2018).

without chest pain. Careful examination or history taking may often reveal other signs of ALS, for example fasciculation or wasting. Finally, Pompe's disease (acid maltase deficiency) typically presents with mixed limb and respiratory muscle weakness, but respiratory symptoms as a cause of presentation are well recognised.

Pre-existing or acquired respiratory muscle weakness can be a cause of failure to wean and is present in approximately 25% of patients who have received invasive mechanical ventilation for a week or more. Features which should alert the clinician to this possibility include low oxygen and pressure requirements, and an inability to trigger the ventilator.

Clinical evaluation

In the history, features suggestive of respiratory muscle weakness are breathlessness that is worse on lying flat or in water, although clinicians should be aware that patients with generalised neuromuscular weakness seldom immerse themselves in water. Breathlessness is also experienced during any action which increases pressure in the abdomen, since diaphragm weakness precludes protecting the intrathoracic cavity from this pressure, everyday examples include bending forward to pick up items from the floor or to tie shoelaces, and getting out of a car as most cars are engineered so that the occupant must bend forward to navigate past the front pillar.

The chest radiograph may show hemidiaphragm elevation, but this can be difficult to distinguish from a poor inspiration. Spirometry tends to show a restrictive pattern, but the upright vital capacity (VC) may be close to or within the normal range until respiratory failure occurs. Patients with diaphragm weakness often have a fall in their VC when in the supine position. In healthy humans this is less than 10%, but occasionally may be in the range 10–20%. In practical terms a normal supine VC excludes respiratory muscle weakness.

Since the lung parenchyma is normal and spirometry is reduced, the classical lung function abnormality is of a reduced TLC with a reduced T_{LCO} but a supernormal K_{CO}. If undertaken, cardiopulmonary exercise testing will show a reduced oxygen uptake (V'_{O_2}max) with ventilatory limitation and possibly hypercapnia.

Bedside tests

Pressures may be measured in the clinic or at the bedside in the mouth or nose. Classically inspiratory muscles are measured during a maximum effort undertaken against a closed shutter from residual volume and the expiratory muscles are tested during a maximum effort, also against a closed shutter, undertaken from TLC. Commercially available equipment for this purpose is easily portable. Alternative causes for low values (other than true weakness) are: inadequate patient effort (whether due to age, cognitive function or willingness to participate); glottic or airway problems, which prevent full transmission of oesophageal pressure to the mouth; or difficulty creating a seal. The latter problem can be overcome by using maximal sniff nasal pressure for the measurement of inspiratory muscle function and the whistle mouth pressure. A more comprehensive picture can be obtained by the use of multiple tests, but caution is advised when focusing exclusively on the values obtained for the following reasons. First, patients with known neurological disease may initially have values within the normal range. Since the range of normal values are wide, this does not exclude the possibility that prior values would have been higher or remove the need for appropriate surveillance. Secondly, mildly low values have been recorded in a range of conditions that are much more common either for physiological reasons (*e.g.* hyperinflation in the case of COPD) or general difficulties achieving a maximal effort in the case of other conditions such as heart failure.

Specialised tests

Occasionally, for clinical or research reasons, a more precise evaluation of diaphragm function is required. Indications for this might be:

- evaluation of hemidiaphragm function; and
- exclusion of respiratory muscle weakness in a patient unwilling or unable to produce a maximum effort.

Tests available include the following.

1) Measurement of transdiaphragmatic pressure (P_{di}) using pressure sensors (most commonly air-filled balloons) per nasally and positioned so that one is above and one below the diaphragm. This procedure eliminates problems of airway or glottic transmission and allows measurement of other items of interest, for instance end-expiratory oesophageal pressure or static lung compliance. Both sniff, cough and maximal static manoeuvres are possible.
2) Phrenic nerve stimulation is a technique that normally uses a magnetic nerve stimulator (although users should be aware this is contraindicated in the presence of implanted ferrous metal) to simulate the phrenic nerves and is thus, in conjunction with measurement of P_{di} or diaphragm electromyography (EMG), suitable for evaluating hemidiaphragm function.
3) Diaphragm EMG can be measured from a surface needle or oesophageal electrodes. Using the latter technique it has been possible to measure diaphragm activity in a range of respiratory diseases and, in conjunction with phrenic nerve stimulation, conduction time (figures 1 and 2). This assessment can be useful in differentiating obstructive and central sleep disordered breathing.

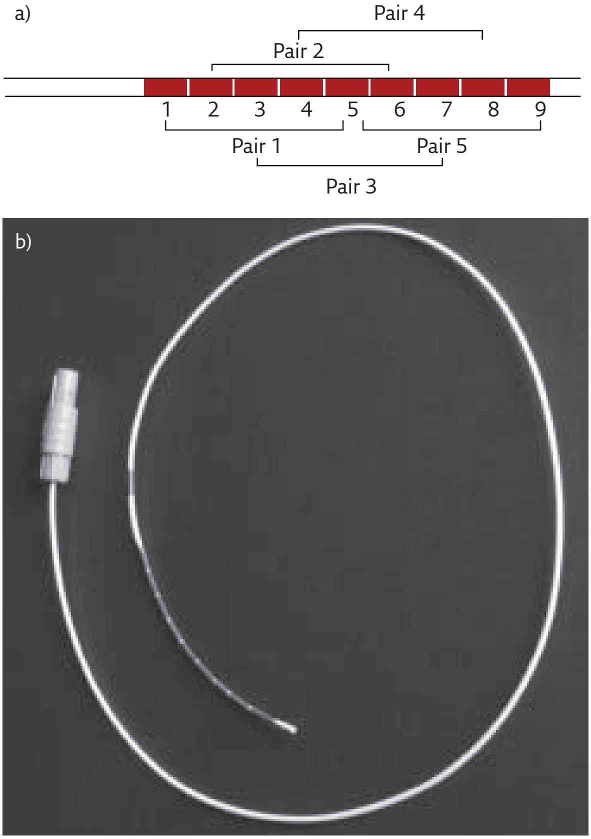


Figure 1. Use of diaphragm EMG and a pressure trace to demonstrate obstructive apnoea: a) configuration, b) multipolar oesophageal electrode catheter. Reproduced from Luo et al. *(2008)* Eur Respir J*; 31: 650–657.*

4) Imaging. Recently ultrasound has been developed as a test of diaphragm function, which by definition can only evaluate each hemidiaphragm separately. The most useful parameter seems to be the degree of fractional shortening, but thickness at resting end expiration is of some value in experienced hands. Measurements can be made during pressure support, but not assist-control ventilation.

Further investigations

There are no further investigations of routine value in the diagnosis of respiratory muscle weakness. Depending on personal preference and clinical features, may clinicians in an outpatient setting will measure creatinine kinase and where it is desirable to exclude myasthenia gravis acetylcholine receptor antibodies and anti-muscle-specific kinase antibodies; however, these two tests between them only cover 99% of cases of myasthenia gravis. Acid maltase can be conveniently excluded with a dried blood spot enzyme assay.

Treatment assessment

Individuals with diaphragm weakness should be advised to keep active and avoid becoming overweight. Positional modification, by sleeping in a semi-recumbent

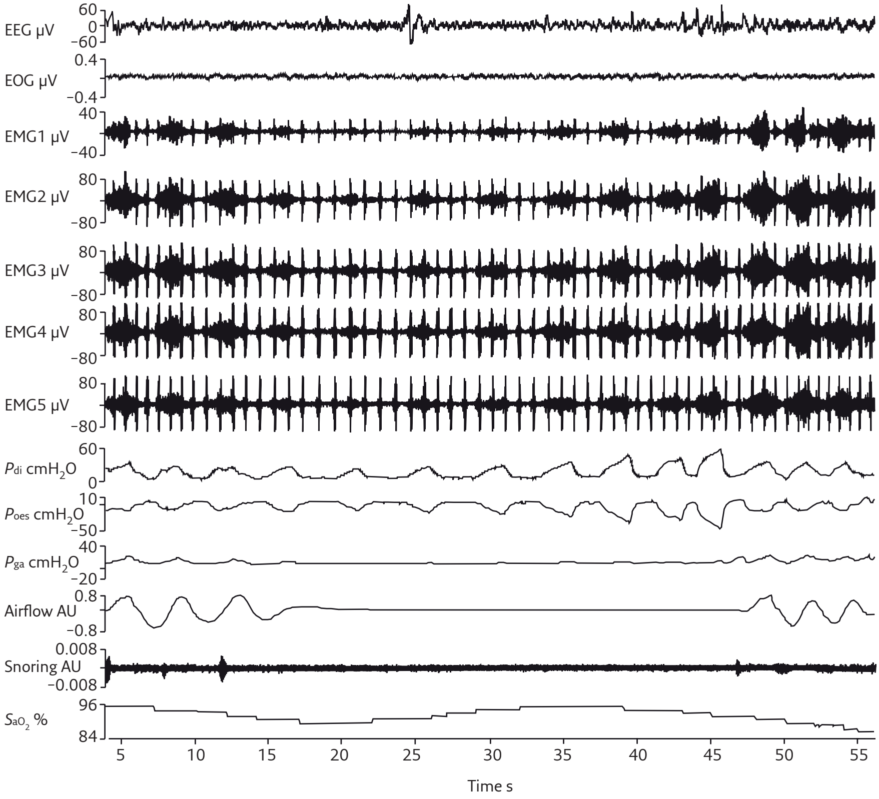


Figure 2. Use of diaphragm EMG and a pressure trace to demonstrate obstructive apnoea: a patient trace. EEG: electroencephalogram; EOG: electro-oculogram; P_{es}: oesophageal pressure; P_{gas}: gastric pressure; AU: arbitrary unit. Reproduced from Luo et al. *(2008)* Eur Respir J*; 31: 650–657.*

position may help the mechanical efficiency of the diaphragm and improve comfort at night. Symptoms of sleep disordered breathing, such as disturbed sleep, waking with a panic sensation, morning headaches and daytime sleepiness, should be sought. The presence of these should prompt the need for a sleep study. Other indications for a sleep study include recurrent chest infections or significantly reduced inspiratory muscle strength.

Sleep studies

The most common abnormal finding is nocturnal hypoventilation with the most prominent dips in S_{aO_2} and peaks in carbon dioxide tension (P_{CO_2}) during rapid eye movement (REM) sleep, as respiratory effort is most dependent on the defective diaphragm at this time. Nocturnal hypoventilation can be detected with respiratory polygraphy or oximetry studies with additional P_{CO_2} monitoring, *e.g.* using a transcutaneous CO_2 system. The extent of sleep disordered breathing is proportional to the degree of inspiratory muscle weakness. It is seen in those with bilateral diaphragm weakness (or if obesity or underlying parenchymal lung disease are present), but sleep disordered breathing can also be found in those with suspected unilateral diaphragm weakness.

NIV

NIV is indicated in patients with symptomatic nocturnal hypoventilation or daytime hypercapnia. CPAP is usually insufficient if there is a significant degree of hypercapnia. Bilevel pressure support ventilation with a back-up rate is the mode of choice, and should be titrated to control respiratory events, S_{aO_2} and P_{CO_2} overnight.

Airway clearance

If diaphragm weakness is due to an isolated phrenic nerve lesion, cough efficacy should be relatively preserved, although individuals with marked inspiratory weakness may develop basal pneumonic collapse and frequent chest infections. Active physiotherapy with a 'huffing' technique may be sufficient to ensure bronchial secretion clearance. In those patients with disorders affecting the diaphragm and expiratory muscle strength, *e.g.* ALS or muscular dystrophy, assessment of cough efficacy is indicated. If cough peak flow is less than 270 $L \cdot min^{-1}$ in adults, then secretion clearance is likely to be reduced at the time of a chest infection. It will be further impaired in those with cough peak flow less than 160 $L \cdot min^{-1}$. For these groups a physiotherapy assessment to provide either an insufflation (ambu-type) bag to help clear secretions or a mechanical insufflator–exsufflator cough assist machine may help, and reduce the frequency and/or severity of chest infections.

Diaphragm pacing

There is no logic to using phrenic nerve pacing in patients with phrenic nerve lesions.

Diaphragm pacing with small electrodes embedded in diaphragmatic muscle has recently been explored in ALS patients with respiratory insufficiency. In a randomised controlled trial of NIV *versus* NIV and pacing (the DiPALS trial), there were excess deaths in the pacing group, so diaphragm pacing cannot be recommended in this condition. There are no large trials in other groups with diaphragm weakness.

Clinical course

Neuralgic amyotrophy tends to recover, but patients should be warned that this may take between 2 and 5 years. Where recovery doesn't occur diaphragm plication may be considered where there is substantial impairment of lung function or frequent chest infections in the presence of radiological atelectasis.

Further reading

- American Thoracic Society/European Respiratory Society (2002). ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med*; 166: 518–624.
- De Jonghe B, *et al.* (2002). Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA*; 288: 2859–2867.
- DiPALS Writing Committee, *et al.* (2015). Safety and efficacy of diaphragm pacing in patients with respiratory insufficiency due to amyotrophic lateral sclerosis (DiPALS): a multicentre, open-label, randomised controlled trial. *Lancet Neurol*; 14: 883–892.
- Engel AG (1970). Acid maltase deficiency in adults: studies in four cases of a syndrome which may mimic muscular dystrophy or other myopathies. *Brain*; 93: 599–616.
- Hughes PD, *et al.* (1999). Long term recovery of diaphragm strength in neuralgic amyotrophy. *Eur Respir J*; 13: 379–384.

- Polkey MI, *et al.* (2017). Respiratory muscle strength as a predictive biomarker for survival in amyotrophic lateral sclerosis. *Am J Respir Crit Care Med*; 195: 86–95.
- Polkey MI (2018). Respiratory muscle assessment in clinical practice. *Clin Chest Med*; 40: 307–315.
- Steier J, *et al.* (2007). The value of multiple tests of respiratory muscle strength. *Thorax*; 62: 975–980.
- Steier J, *et al.* (2008). Sleep-disordered breathing in unilateral diaphragm paralysis or severe weakness. *Eur Respir J*; 32: 1479–1487.

Pleural effusion

Robert Loddenkemper and Julius Janssen

Pleural effusion is defined as accumulation of fluid in the pleural space that exceeds the physiological amounts of 10–20 mL. Pleural effusion develops either when the formation of pleural fluid is excessive or when fluid resorption is disturbed. Pleural effusions may represent a primary manifestation of many diseases but most often, they are observed as secondary manifestations or complications of other diseases.

Pleural effusion is found in almost 10% of patients who have internal diseases and the main cause in 30–40% of these is cardiac failure. Among the noncardiac effusions, parapneumonic effusions are the most common at 36%, of which ~75% are of bacterial and 25% of viral origin. Malignant pleural effusions follow in 18% of cases,

Key points

- Pleural effusions may present as primary manifestations of many diseases. However, most often, they are observed as secondary manifestations or complications of other diseases.
- Cardiac failure (transudative effusion) is the main cause of pleural effusions. Of noncardiac exudative causes, parapneumonic effusions are commonest, followed by malignant pleural effusions and pleural effusions due to pulmonary embolism. Mixed causes of exudative and transudative effusions occur frequently, and may present as a transudate.
- Pleural effusion can, in most cases, be diagnosed by case history, clinical presentation, imaging techniques and examination of pleural fluid. Small pleural effusions can be detected best by ultrasound (or CT).
- The most important laboratory parameter of pleural fluid is total protein, distinguishing transudates from exudates.
- Biopsy procedures such as thoracoscopy or ultrasound-guided closed-needle biopsy may be necessary to confirm or exclude a malignant cause. Adenosine deaminase level in pleural fluid can be helpful to confirm or exclude the diagnosis of pleural TB.
- Treatment options for malignant pleural effusion include therapeutic thoracentesis, chemical pleurodesis by talc slurry through a chest tube or thoracoscopy and talc poudrage. An alternative is permanent drainage by an indwelling pleural catheter. Treatment of malignant pleural effusion depends on the underlying disease; survival can be predicted by the LENT score.

half of which are caused by lung or breast cancer. Pleural effusion is secondary to pulmonary embolism in 14% of cases, to liver cirrhosis in 5% and to gastrointestinal diseases, mainly pancreatitis, in 2% of cases. Many other possible causes, such as collagen vascular diseases like rheumatoid arthritis and systemic lupus erythematosus as well as several drugs (www.pneumotox.com), play an important role in differential diagnosis. Often, pleural effusions are observed after abdominal surgery, liver transplantation or coronary artery bypass surgery/pericardiectomy.

Pleural effusion may result from a number of pathophysiological mechanisms, all of which disturb the physiological balance between the formation and removal of pleural fluid (normal production estimated at 15 $\text{mL} \cdot \text{day}^{-1}$ in a 60-kg person). Most effusions develop from both an increase in the entry rate of liquid into the pleural space and a decrease in the maximal exit rate of liquid from the pleural space. Transudative effusions are caused either by increased hydrostatic pressure (*e.g.* in cardiac failure) or by reduced plasma oncotic pressure because of protein deficiency (*e.g.* liver cirrhosis or nephrotic syndrome). The pleura itself remains intact. Rarely, transudates may arise from the entry of liquids with low protein concentrations (*e.g.* urine, cerebrospinal fluid or iatrogenic intrapleural infusion of fluids). In contrast, pathological changes in the pleura result in exudative effusions caused by a diffuse increase of capillary permeability, due to localised ruptures (*e.g.* blood vessels, lymphatic vessels, lung abscess or oesophagus) or to disturbed absorption (*e.g.* lymphatic blockage). In a significant number of patients, pleural effusion is caused by two diseases at the same time, of which heart failure is one in the majority of cases. In these cases, an exudative cause like malignant effusion may not be recognised because of the transudative presentation during analysis.

Pleural effusion may present at all ages but is mainly found in adults. Malignant pleural effusions are observed predominantly in patients aged >60 years. In 25% of patients diagnosed with malignant pleural effusion, this is the first presentation of cancer.

The most common clinical presentations are dyspnoea and chest pain, and those of the individual underlying diseases. Physical examination reveals dullness on percussion, usually at the base of the thorax, and decreased breath sounds.

Pleural effusion may be demonstrated by several techniques with different sensitivities. The demonstration by percussion requires at least 300–400 mL of fluid, whereas at least 200–300 mL is necessary for standard chest radiography. Smaller amounts (>50 mL) can be recognised by lateral decubitus radiography, which also demonstrates whether the fluid is moving freely. Ultrasound can demonstrate small effusions and the sensitivity if this is almost 100% for volumes of ≥100 mL. CT and MRI have very similar sensitivities but require more advanced technology and are therefore much more expensive. However, if pulmonary embolism is suspected, CT angiography is the preferred test.

In most cases, the aetiology is determined based on the case history, clinical presentation, imaging techniques and examination of the pleural fluid. The rate of onset is important in the differentiation of the possible cause: rapidly developing effusions (within days) can be attributed to a limited number of causes, mostly infection, embolism or chest trauma; a more slowly evolving effusion is more likely to be caused by a chronic process, like malignancy or TB.

The presence of a pleural effusion is established by thoracentesis. The site should be selected according to the results of the diagnostic procedures. Preferably, thoracentesis should be performed under ultrasound guidance, as this will reduce the number of complications. Thoracentesis is indicated in all cases of pleural effusion of unknown origin of over 1–2 cm in diameter and in effusions that do not resolve after appropriate treatment. Additional biopsy procedures may be necessary to confirm or exclude malignant or tuberculous causes. These are performed in a stepwise diagnostic approach (figure 1). Thoracoscopy is the gold standard of pleural tissue diagnosis, and preferred over closed pleural biopsy because of the higher diagnostic yield and lower number of complications.

In many cases, evaluation of the pleural fluid yields valuable diagnostic information or even permits a clear diagnosis, although a specific benign diagnosis is rare in the case of an exudate. The most important criteria are appearance, protein content and cellular components. In the case of more specific diagnostic questions, routine measurement of the glucose content is supplemented by determination of further laboratory parameters and a search for infecting organisms (table 1).

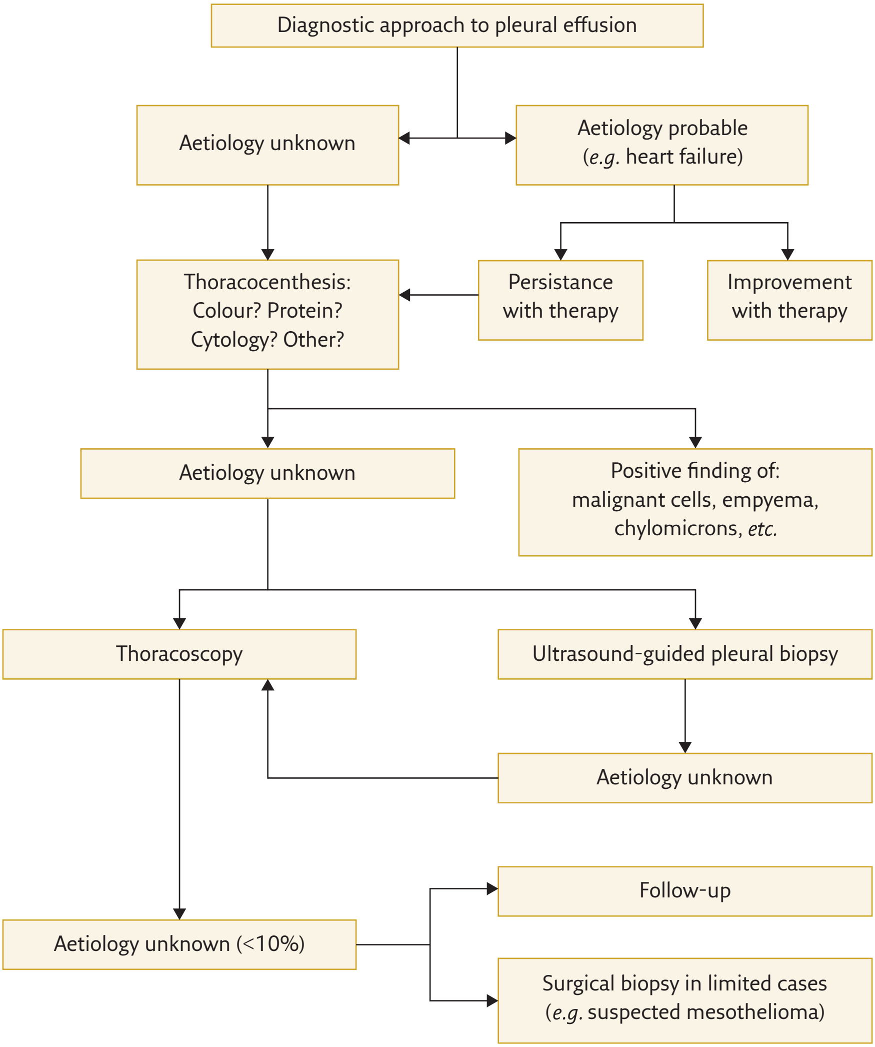

Diagnostic approach to pleural effusion
Aetiology unknown
Aetiology probable (*e.g.* heart failure)
Thoracocenthesis: Colour? Protein? Cytology? Other?
Persistance with therapy
Improvement with therapy
Aetiology unknown
Positive finding of: malignant cells, empyema, chylomicrons, *etc.*
Thoracoscopy
Ultrasound-guided pleural biopsy
Aetiology unknown
Follow-up
Aetiology unknown (<10%)
Surgical biopsy in limited cases (*e.g.* suspected mesothelioma)

Figure 1. Diagnostic approach to pleural effusions.

Table 1. Investigative parameters of pleural effusion

Obligatory
- Appearance
- Total protein
- Cell differentiation (cytology)

Optional
- Glucose (pH)
- Lactate dehydrogenase
- Cholesterol
- NT-proBNP
- Triglycerides
- Amylase
- Bilirubin
- Creatinine
- Haematocrit
- Immunocytology
- Tumour markers
- Adenosine deaminase
- Interferon-γ release assay
- Antinuclear factor, rheumatoid factors, *etc.*
- Search for infecting organisms
  - *Mycobacterium tuberculosis*
  - Gram staining
  - Anaerobic, aerobic bacteria
  - Fungi, parasites

NT-proBNP: N-terminal pro-brain natriuretic protein.

The most important laboratory parameter is the total protein content of the effusion, for which a threshold value of 30 $g \cdot L^{-1}$ differentiates a transudate from an exudate. However, this value is not exclusive, and additional parameters such as lactate dehydrogenase (>200 $U \cdot L^{-1}$) or cholesterol (>0.55 $mmol \cdot L^{-1}$ (60 $mg \cdot dL^{-1}$)) may be helpful (table 2). The simultaneous determination of serum values is important, because these may strongly influence the values in the pleura. Low glucose values may indicate rheumatoid pleuritis, lupus pleuritis, empyema, TB or malignant effusion, or oesophageal perforation. Elevated levels of N-terminal pro-brain natriuretic protein (in pleural fluid and/or blood) are characteristic of effusions caused by cardiac failure.

Markedly elevated amylase values are observed in acute pancreatitis and pancreatic pseudocysts, oesophageal perforation and, occasionally, in malignant effusions.

Haemothorax is characterised by purely bloody effusions and haematocrit values >50% of those in peripheral blood.

Table 2. Light's criteria for exudates

	Effusion concentration	Effusion/serum concentration ratio	Sensitivity	Accuracy
Total protein	>30 $g \cdot L^{-1}$	>0.5	89.5%	95.4%
Lactate dehydrogenase	>200 $U \cdot L^{-1}$	>0.6	91.4%	94.7%

In chylothorax, the pleural effusion has usually a typical milky and opalescent appearance. Increased triglycerides distinguish chylous from pseudochylous effusions.

In an endemic area of TB, an elevated adenosine deaminase (ADA) level (>50 U·L^{-1}) can be considered as confirmation of the diagnosis of TB. In a nonendemic area, TB is virtually excluded if the ADA level is <35 U·L^{-1}. Diagnostic testing for the infecting organisms that cause pleural effusion is indicated in parapneumonic effusions/ empyemas with aerobic and anaerobic cultures, and in suspected tuberculous, fungal or parasitic effusions. Simultaneous use of blood culture may increase the microbiological yield by 20%.

Therapeutic aims in patients with pleural effusion are palliation of symptoms (pain and dyspnoea), treatment of the underlying diseases, prevention of trapped lung with reduction of pulmonary function, and prevention of recurrences. The therapeutic approach depends on the expected survival, which can be predicted by the LENT score (pleural fluid lactate dehydrogenase, Eastern Cooperative Onology Group performance score, serum neutrophil/lymphocyte ratio, tumour type)

Pleural infection (empyema and parapneumonic effusion with pH < 7.20) requires besides antibiotic treatment, additional pleural drainage. Resolution is facilitated by instillation of tissue plasminogen activator and DNAse, which reduces mortality and the need for surgery. The instillation of a fibrinolytic agent alone has not proven to be helpful.

In malignant pleural effusions, therapeutic thoracentesis may be the only intervention in frail patients with limited life expectancy or in patients who are expected to improve from chemotherapy (for small cell lung cancer or lymphoma) or targeted therapy. Chemical pleurodesis can be obtained by chest-tube drainage combined with talc slurry or thoracoscopy with talc poudrage, with a success rate of up to 70%. Permanent removal of pleural fluid may be obtained with the use of an indwelling pleural catheter. This may lead to spontaneous pleurodesis in 45% of cases.

Further reading

- Arnold DT, *et al.* (2015). Pleural fluid adenosine deaminase (Pfada) in the diagnosis of tuberculous effusion in a low incidence population. *PLoS ONE* 10; e011304.
- Bhatnagar R, *et al.* (2015). The modern diagnosis and management of pleural effusions. *BMJ*; 351: h4525.
- Bhatnagar R, *et al.* (2016). Advanced medical interventions in pleural disease. *Eur Respir Rev*; 25: 199–213.
- Bhatnagar R, *et al.* (2018). Outpatient talc administration by indwelling pleural catheter for malignant effusion. *N Eng J Med*; 37: 1313–1222.
- Bintcliffe OJ, *et al.* (2016). Unilateral pleural effusions with more than one apparent etiology: a prospective observational study. *Ann Am Thorac Soc*; 13: 1050–1056.
- Davies HE, *et al.* (2011). The diminishing role of surgery in pleural disease. *Curr Opin Pulm Med* 2011; 17: 247–254.
- DePew ZS, *et al.* (2014). Feasibility and safety of outpatient medical thoracoscopy at a large tertiary medical center. A collaborative medical-surgical initiative. *Chest* 2014; 146: 398–405.
- Haas AR, *et al.* (2014). Advances in pleural disease management including updated procedural coding. *Chest* 2014; 146: 508–513.

- Hooper CE, *et al.* (2010). Setting up a specialist pleural disease service. *Respirology* 2010; 15: 1028–1036.
- Hooper C, *et al.* (2010). Investigation of a unilateral pleural effusion in adults: British Thoracic Society pleural disease guideline 2010. *Thorax*; 65: Suppl. 2, ii4–ii17.
- Idell S, *et al*. (2018). Intrapleural fibrinolytic therapy for empyema and pleural loculation: knowns and unknowns. *Ann Am Thorac Soc*; 15: 515–517.
- Koegelenberg CF, *et al*. (2015). The utility of ultrasound-guided thoracocenthesis and pleural biopsy in undiagnosed pleural exudates. *Thorax*; 70: 995–997.
- Krochmal R, *et al.* (2016). Patient evaluation for rapid pleurodesis of malignant pleural effusions. *J Thorac Dis*; 8: 2538–2543.
- Clive AO, *et al.* (2014). Predicting survival in malignant pleural effusion: development and validation of the LENT score. *Thorax*; 69: 1098–1104.
- Piccolo F, *et al.* (2014). Intrapleural tissue plasminogen activator and deoxyribonuclase for pleural infection. *Ann Am Thorac Soc*; 11: 1419–1425.
- Porcel JM, *et al.* (2015). The diagnosis of pleural effusions. *Expert Review Respir Med*; 9: 801–815.
- Psallidas I, *et al.* (2016). Malignant pleural effusion: from bench to bedside. *Eur Respir Rev*; 25: 189–198.
- Wang Z, *et al.* (2015). Diagnostic value and safety of medical thoracoscopy in tuberculous pleural effusion. *Respir Med* 2015; 109: 1188–1192.

Pneumothorax and pneumomediastinum

Julius Janssen

Pneumothorax

Pneumothorax is defined as a collection of air in the pleural space due to collapse of the lung. The expansion of the lung is maintained by the negative pressure in the virtual pleural space and due to the elastic recoil pressure, the lung will collapse in if the negative pressure drops. This can be caused by an open-air connection of the chest wall, which can be traumatic or iatrogenic. Mostly, a pneumothorax occurs by an air leak in the visceral pleural due to trauma, barotrauma or iatrogenic (baro)trauma. In the majority of cases, a pneumothorax occurs spontaneously. This chapter will focus on spontaneous pneumothorax.

Epidemiology

The incidence of spontaneous pneumothorax is estimated at 22 cases per 100000 inhabitants, with a male/female ratio of about 3/1. Traditionally, spontaneous pneumothorax is subdivided into primary spontaneous pneumothorax (PSP), occurring in young (smoking) patients with no underlying lung disease, and secondary spontaneous pneumothorax (SSP), which occurs in older patients with underlying lung disease, mostly COPD. The former assumption of a bimodal age distribution, with a peak of PSP between 20 and 30 years, and a peak of SSP in patients >50 years, has not been confirmed in recent large epidemiology studies. The distinction between PSP and SSP is becoming increasingly blurred. This classification is now subject to criticism and may be replaced in the future.

Smoking is the most important risk factor for spontaneous pneumothorax. >80% of patients with spontaneous pneumothorax are current or former smokers. The relative risk of contracting a spontaneous pneumothorax is estimated to be 10–20-fold increased compared with nonsmokers. Besides, there is a dose–response relationship. Smoking cessation will reduce the risk of spontaneous pneumothorax substantially. In addition, the smoking of cannabis increases the risk of spontaneous pneumothorax.

Key points

- The cause of spontaneous pneumothorax is not clear.
- The traditional distinction between primary and secondary spontaneous pneumothorax is subject to discussion.
- The treatment of spontaneous pneumothorax is subject to debate.
- Treatment of spontaneous pneumothorax should be focused on outpatient management, unless recurrence prevention is included in the treatment.

Cannabis causes an accelerated bullous deformation in the apex of the lungs. Other risk factors are height and male sex.

Cases of PSP tend to occur in clusters. This has been attributed to changes in atmospheric pressure, although these changes are much more limited compared to air pressure changes during aeroplane flight, which are not associated with risk of spontaneous pneumothorax.

Catamenial pneumothorax is related to menses in women of reproductive age and may account for ~5% of PSP cases in women, although some studies indicate a higher incidence. Catamenial pneumothorax is associated with thoracic endometriosis, although this can only be proven by pleural biopsy in a minority of cases.

Tension pneumothorax occurs when the intrapleural pressure becomes greater than the atmospheric pressure during the whole cycle of respiration. This is a life-threatening situation, which occurs mostly after trauma or during mechanical ventilation. Tension pneumothorax is extremely rare in spontaneous pneumothorax.

Causes

The cause of spontaneous pneumothorax is unknown. With increasing use of imaging techniques, it has been demonstrated that in almost all cases of spontaneous pneumothorax, an emphysema-like deformation of the lung parenchyma can be demonstrated in the apical part of the lung. This deformation consists of blebs and/or bullae, also called ‘emphysema-like changes’ (ELCs). There has been a general belief that spontaneous pneumothorax is caused by rupture of these ELCs but this has never been proved. During thoracoscopic inspection of the ELCs in patients with spontaneous pneumothorax, a rupture of an ELC is hardly ever demonstrated. Another theory about the cause of spontaneous pneumothorax is the presence of pleural pores in the visceral pleura, leading to pleural porosity. The finding of ELCs in almost all spontaneous pneumothorax patients supports the idea that there is a continuum between PSP and SSP, and these are not separate diseases that require separate management.

Clinical presentation

The most frequent presenting symptoms of spontaneous pneumothorax are acute onset of chest pain, sometimes shoulder pain and dyspnoea. Symptoms may be almost absent but in patients with COPD, dyspnoea may be predominant or even severe, which may require immediate intervention, mostly chest tube drainage of the affected side.

Imaging

The diagnosis of spontaneous pneumothorax is confirmed by imaging. The standard imaging technique is the posterior–anterior inspiratory chest radiograph (figure 1). This will demonstrate displacement of the pleural line, and absence of lung tissue between the pleural line and the chest wall. CT scanning of the chest is more sensitive than chest radiography, especially in cases of small spontaneous pneumothoraces, but rarely necessary to confirm the diagnosis. The role of ultrasound in the diagnosis of pneumothorax is emerging, especially in emergency and intensive care departments. The role of ultrasound in the standard diagnostic workup of spontaneous pneumothorax has not been not established.

Treatment

The treatment of spontaneous pneumothorax is subject to discussion, characterised by a lack of consensus and may vary from outpatient observation to surgical intervention.

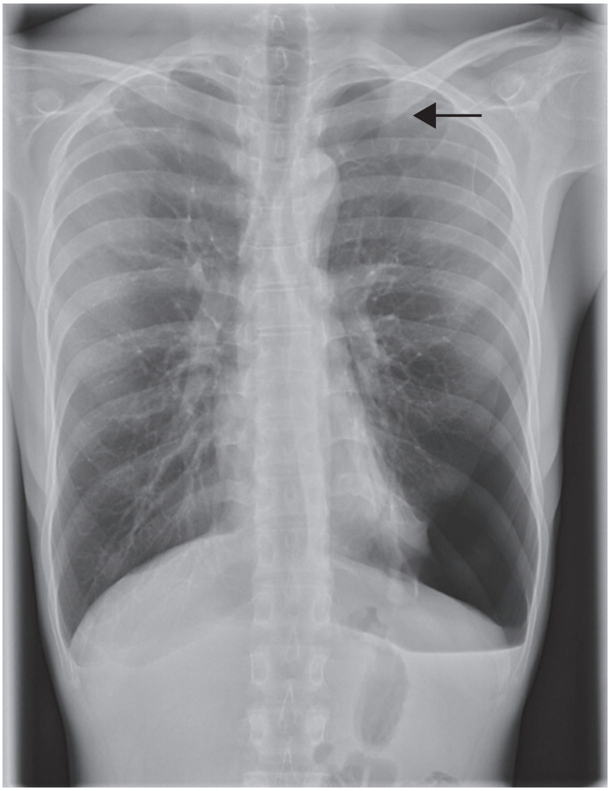


Figure 1. Left-sided, large pneumothorax. Note the bullous deformation at the apex of the lung (arrow) and the pleural fluid at the bottom.

Important reasons for the lack of consensus are:

- The number of high-quality randomised studies is limited and there is consequently a paucity of evidence.
- The existing guidelines agree about the definition of the size of a large pneumothorax in <50% of cases, which results in variation of the subsequent treatment options.
- A large number of treatment options is available, ranging from observation, manual aspiration, ambulatory treatment with small catheter attached to a Heimlich valve, chest tube insertion with/without suction and with/without pleurodesis, to thoracoscopy with talc pleurodesis, and surgical treatment with (partial) pleurectomy, pleural rubbing, and/or resection of blebs and bullae.

The traditional initial treatment was hospitalisation with chest tube drainage and underwater seal suction in cases of a large pneumothorax, and observation in cases of a small pneumothorax. The important disadvantages of chest tube drainage are an invasive procedure (insertion of a chest tube), and hospitalisation and immobilisation of the patient. The 1-year success rate of chest tube treatment is the same as the success rate of manual aspiration and is ~70%.

Manual aspiration of air can be performed in the emergency department or can be performed as outpatient treatment in ~50% of patients. In cases of failure, a second potentially successful attempt can be performed after a few hours. Recent data show that manual aspiration can also be performed in SSP patients with the same result as obtained in PSP.

An alternative between manual aspiration and chest tube treatment is ambulatory treatment with insertion of a small (6–8 French) catheter attached to a Heimlich valve. Trials have shown a success rate of 80%.

Observation alone may be the preferred treatment in small (apical) pneumothorax in a patient with limited symptoms. The place of observation in large spontaneous pneumothorax is currently subject to research.

Thoracoscopy and talc poudrage (2 g graded talc) is an in-hospital procedure that requires general anaesthesia because of the very painful reaction of talc on the parietal pleura. The hospital stay can be short, with chest tube removal and discharge the day after thoracoscopy, in cases of complete re-expansion of the lung and absence of persisting air leakage.

Surgical treatment of spontaneous pneumothorax is indicated only in cases where less invasive procedures have failed. It consists of a video-assisted thoracoscopic surgery (VATS) procedure with one to three ports under general anaesthesia in a (selectively) intubated patient. The surgical procedure consists of pleural rubbing, abrasion, a (partial) pleurectomy or talc insufflation to prevent recurrence of spontaneous pneumothorax. ELCs in the apex of the lung with a visible leak are resected. The vast majority of ELCs do not leak, and the role of their resection is not clear, and subject to discussion between pulmonologists and surgeons.

How to choose the appropriate treatment

The decision of how to treat pneumothorax depends on clinical symptoms, the episode of the spontaneous pneumothorax (first or recurrent) and the willingness of the patient to accept a risk of recurrence after treatment. Treatment options can be categorised as aiming at lung re-expansion only (observation, manual aspiration, ambulatory catheter with Heimlich valve or chest tube drainage) or lung re-expansion and recurrence prevention (thoracoscopy and talc pleurodesis, or surgical treatment).

Choosing the right treatment for the right patient is difficult, as we do not know how to identify patients who have a high risk of recurrence. If recurrence prevention is not required, outpatient observation may be good choice in cases with few symptoms and an incomplete collapse of the lung. In cases of symptomatic spontaneous pneumothorax and significant collapse of the lung, manual aspiration is the preferred option over chest tube drainage because the 1-year success is the same, and manual aspiration does not require (long) hospitalisation, is not an invasive procedure and has fewer complications. If recurrence prevention is required, thoracoscopy and talc pleurodesis or VATS including pleurectomy or talc pleurodesis are indicated. For every patient, it is important to stop smoking as this has been shown to significantly reduce the risk of recurrence.

Pneumomediastinum

Pneumomediastinum is defined as the presence of air the mediastinum and is also known as mediastinal emphysema. Spontaneous pneumomediastinum (SPM) may develop without obvious aetiology but underlying lung diseases such as asthma and fibrosis have often been reported. Secondary pneumomediastinum is caused by barotrauma (*e.g.* mechanical ventilation) or penetrating trauma to the chest.

Spontaneous pneumomediastinum is a rare condition with a reported incidence ranging from one in 800 to one in 42000 of all patients presenting at the hospital emergency department.

Pneumomediastinum results from rupture of alveoli, allowing free air to enter the mediastinum and the hilum. The most common presenting symptom is chest pain. On physical examination, there is sometimes a positive 'Hamman's sign'. This phenomenon was first described in 1937 as a crunching, bubbling, popping, crackling or clicking sound synchronous with the heartbeat caused by the heart beating against air-filled pockets.

There are several typical chest radiographic signs: lucent streaks or bubbles of gas that outline mediastinal structures and elevate the mediastinal pleura, which may extend into the neck or chest wall; and mediastinal gas outlining the superior surface of the diaphragm and separating it from the heart (continuous diaphragm sign).

CT is more sensitive than plain chest radiographs in detecting SPM but many SPMs detected only by CT are small and clinically insignificant.

A triggering event can be identified in most cases. SPM can be triggered by voluntary alteration in breathing pattern, like smoking of cannabis, pulmonary function testing or playing a wind instrument. Involuntary alteration of breathing pattern (vomiting, coughing, childbirth or athletic competition) are also known to be able to provoke incidentally a pneumomediastinum in patients without an underlying disease.

The management of a pneumomediastinum is conservative since it is a benign, spontaneously resolving disease. After recovery, restriction of physical exercise is unnecessary.

Further reading

- Bintcliffe O, *et al.* (2015). Spontaneous pneumothorax: time to rethink management. *Lancet Respir Med*; 3: e36.
- Bobbio A, *et al.* (2015). Epidemiology of spontaneous pneumothorax: gender related differences. *Thorax*; 70: 653–658.
- Bridevaux P, *et al.* (2011). Short-term safety of thoracoscopic talc pleurodesis for recurrent primary spontaneous pneumothorax: a prospective European multicentre study. *Eur Respir J*; 38: 770–773.
- Hallifax R, *et al.* (2017). Effectiveness of chemical pleurodesis in spontaneous pneumothorax recurrence prevention: a systematic review. *Thorax*; 72: 1121–1131.
- Janssen J, *et al.* (2011). Primary spontaneous pneumothorax: towards outpatient treatment and abandoning chest tube drainage. *Respiration*; 82: 201–203.
- Maskell NA (2017). Pneumothorax management: time to improve the evidence base. *Thorax*; 72: 1065–1066.
- Massongo M, *et al.* (2014). Outpatient management of primary spontaneous pneumothorax: a prospective study. *Eur Respir J*; 43: 582–590.
- Mihos P, *et al.* (2004). Sports-related spontaneous pneumomediastinum. *Ann Thorac Surg*; 78: 983–986.
- Thelle A, *et al.* (2017). Randomised comparison of needle aspiration and chest tube drainage in spontaneous pneumothorax. *Eur Respir J*; 49: 1601296.
- Tschopp JM, *et al.* (2015). ERS task force statement: diagnosis and treatment of primary spontaneous pneumothorax. *Eur Respir J*; 46: 321–335.
- Tschopp JM, *et al.* (2017). Spontaneous pneumothorax: stop chest tube as first-line therapy. *Eur Respir J*; 49: 1700306.

Mediastinitis

Pierre-Emmanuel Falcoz, Nicola Santelmo, Anne Olland
and Gilbert Massard

The majority of acute mediastinal infections results from oesophageal perforation or infection following a trans-sternal cardiac procedure. Occasionally, acute mediastinitis results from oropharyngeal abscesses with severe cervical infection spreading along the fascial planes into the mediastinum. This particularly virulent form of mediastinal infection is described as descending necrotising mediastinitis (DNM).

DNM is a potentially lethal condition especially if diagnosis or treatment is delayed or inappropriate. Despite the introduction of modern antimicrobial therapy and CT imaging, DNM has continued to produce high mortality rates (reported between 25% and 40%), mainly relying on earliness of diagnosis.

Criteria for diagnosis of DNM

Criteria for diagnosis of DNM have been accurately defined as follows.

- Clinical manifestations of a severe infection
- Establishment of a relationship between an oropharyngeal or cervical infection and subsequent mediastinitis
- Demonstration of radiographic features characteristic of DNM
- Documentation of a necrotising mediastinal infection at the time of operative debridement or necropsy

Epidemiology

Primary sites of infection are periodontal, retropharyngeal and peritonsillar abscesses. According to Wheatley *et al.* (1990), the most common primary oropharyngeal infection is odontogenic (25 out of 43 cases), with mandibular or molar abscesses being the second and third most common primary infections, respectively.

Key points

- Descending necrotising mediastinitis (DNM) is a particularly virulent and potentially lethal mediastinal infection.
- Initial presentation is toxic shock and respiratory difficulty, sometimes with other signs such as erythema and oedema of the neck and upper chest.
- DNM is an emergency, and should be treated with broad-spectrum intravenous antibiotics as well as early and aggressive surgical drainage.

Route of diffusion

Familiarity with the cervical fascial planes is essential to understanding the propagation pathways, symptoms and thoracic complications of cervical infections. The infection spreads from neck to mediastinum along three primary routes: *via* the retropharyngeal space, the perivascular space and the pre-tracheal space. The retropharyngeal space has been thought to be the most important route by which a cervical infectious disease spreads to the mediastinum (70% of cases in the series of Moncada *et al.* 1978). Rapid spread of infection is facilitated by tissue necrosis (loss of anatomical structure), gravity and negative intrathoracic pressure.

Pathogens involved

DNM is a polymicrobial process with anaerobic organisms being the most predominant. Freeman *et al.* (2000) reviewed the English literature and found 96 patients with DNM between 1990 and 1999. All but four (4%) had mixed aerobic and anaerobic infection, with those pathogens often acting synergistically; in the four exceptions, the sole pathogen was β-haemolytic *Streptococcus*. Chow *et al.* (1978) reported that anaerobes had been recovered from 94% of patients with DNM; 52% had mixed infections and 88% had polymicrobial infections. The presence of *Klebsiella* ssp. is considered as a risk factor of severe disease.

Clinical and radiological signs

The anamnesis of mediastinitis is as follows.

- Phase I: periodontal or peritonsillar abscess treated by simple antibiotherapy
- Phase II: erythema and oedema of the neck with or without associated with subcutaneous emphysema
- Phase III: acute aggravation of the infectious syndrome; onset of cough, dyspnoea, sternal pain and painful dysphagia

Patients with DNM usually present with toxic shock and respiratory difficulty. Other presenting signs may include erythema and oedema of the neck and upper chest. In severe infections, frank necrosis of the skin, fascia and muscle may be present. In the chest, DNM may produce abscesses and empyema, pleural and pericardial effusions, intrathoracic haemorrhage, and cardiac tamponade, and frequently results in the death of the patient.

Delay of diagnosis is one of the primary reasons for the high mortality in DNM. Diagnosis of DNM from conventional radiographic studies may be difficult, principally because the signs appear late in the course of the disease. Cervicothoracic CT imaging is currently considered the diagnostic study of choice for patients in whom DNM is suspected. Indeed, CT scan findings have been proven to confirm the diagnosis of DNM with high accuracy in these patients who often have a nonspecific constellation of symptoms. Various CT imaging findings are increased attenuation of mediastinal fat, air fluid levels, pleural and pericardial effusions, oesophageal thickening, and enlarged lymph nodes. Brunelli *et al.* (1996) found cervicothoracic CT imaging to be immediately diagnostic in all patients in whom it was used.

Treatment

The principles of treatment are as follows.

- Emergency
- Intravenous broad-spectrum antibiotic therapy: probabilistic and secondarily adapted to the pathogen(s)
- Early and aggressive surgical drainage: extensive debridement, excision of necrotic tissue, bacteriological sampling, mediastinal and pleural irrigation, and feeding jejunostomy

The decision on the type of surgical drainage to be employed is a crucial one. Classically, four approaches have been reported:

1) transcervical
2) standard posterolateral thoracotomy
3) median sternotomy
4) transthoracic *via* subxyphoid or clamshell incision

A thoracoscopic approach and video-assisted mediastinoscopic drainage can also be used. Although each of these techniques offers potential advantages and disadvantages, the posterolateral thoracotomy incision (sometimes bilateral) remains the standard by which other transthoracic approaches should be measured.

The optimal surgical approach for mediastinal drainage is theoretically dependent on the level of diffusion of the necrotising process. Several studies have reported that mediastinal drainage is best accomplished through a transthoracic approach when the necrotising process extends below the level of the fourth thoracic vertebra posteriorly or the tracheal bifurcation anteriorly. However, because of the rapid spread of this type of infection, other investigators have advocated mandatory transthoracic mediastinal exploration regardless of the level of infection. This latter point was confirmed in a meta-analysis, where a statistically significant difference ($p<0.05$) in survival was found between patients undergoing transcervical mediastinal drainage (53%) *versus* those receiving transthoracic mediastinal drainage (81%).

Close-watch care

Recurrent abscesses and collections are common after first operative drainage (50%) and they should be drained promptly. Ideally, CT or, failing that, ultrasound-guided percutaneous drainage of recurrent abscesses and collections may decrease the need for recurrent surgical procedures in these critically ill patients. Surveillance should be continued until no evidence of progressive infection is found on CT imaging and the patient displays no clinical signs of infection. Hyperbaric oxygen therapy has not shown any real proof of effectiveness in this particular framework, when looking at evidence-based medicine. It should not take the place of or delay surgical treatment.

Mediastinal fibrosis

Fibrosing mediastinitis is an uncommon chronic sequela of prior infectious mediastinal involvement. A chronic, noninfectious inflammatory process results in progressive mediastinal fibrosis. The fibrosis may constrict or obstruct virtually any of the mediastinal organs (in particular, the superior vena cava, oesophagus and pulmonary vein or artery). CT scans demonstrate a localised (or less frequently diffuse) mass infiltrating the mediastinum and constricting the structure; extensive calcification is associated with the fibrotic mass in the vast majority of the cases. This appearance is pathognomonic of the disorder.

Conclusion

DNM is caused by downward spread of neck infections and constitutes a highly fatal complication of oropharyngeal lesions. CT imaging should be performed in all patients with persistent symptoms of septicaemia after being treated for oropharyngeal infections. Prompt surgical drainage of the mediastinum should be performed. The optimal mediastinal drainage method should be tailored to each patient's condition and extension of the mediastinitis (posterolateral thoracotomy is frequently required). In the post-operative period, progression of the disease and effectiveness of surgical therapy should be monitored by CT. Further drainage should be carried out if necessary either surgically or by percutaneous drainage.

Further reading

- Brunelli A, *et al*. (1996). Descending necrotizing mediastinitis: cervicotomy or thoracotomy? *J Thorac Cardiovasc Surg*; 111: 485–486.
- Celakovsky P, *et al*. (2014). Deep neck infections: risk factors for mediastinal extension. *Eur Arch Otorhinolaryngol*; 271: 1679–1683.
- Chow AW, *et al*. (1978). Orofacial odontogenic infections. *Ann Intern Med*; 88: 392–402.
- Corsten MJ, *et al*. (1997). Optimal treatment of descending necrotizing mediastinitis. *Thorax*; 52: 702–708.
- Devaraj A, *et al*. (2007). Computed tomography findings in fibrosing mediastinitis. *Clin Radiol*; 62: 781–786.
- Erkmen CP, *et al*. (2012). Use of cervicothoracic anatomy as a guide for directed drainage of descending necrotizing mediastinitis. *Ann Thorac Surg*; 93: 1293–1294.
- Estera AS, *et al*. (1983). Descending necrotizing mediastinitis. *Surg Gynecol Obstet*; 157: 545–552.
- Freeman RK, *et al*. (2000). Descending necrotizing mediastinitis: an analysis of the effects of serial surgical debridement on patient mortality. *J Thorac Cardiovasc Surg*; 119: 260–267.
- Haremza C, *et al*. (2011). Successfully treated descending necrotizing mediastinitis through thoracotomy using a pedicled muscular serratus anterior flap. *Interact Cardiovasc Thorac Surg*; 13: 456–458.
- Kocher GJ, *et al*. (2012). Diffuse descending necrotizing mediastinitis: surgical therapy and outcome in a single-centre series. *Eur J Cardiothorac Surg*; 42: e66–e72.
- Marty-Ané CH, *et al*. (1999). Management of descending necrotizing mediastinitis: an aggressive treatment for an aggressive disease. *Ann Thorac Surg*; 68: 212–217.
- Moncada R, *et al*. (1978). Mediastinitis from odontogenic and deep cervical infection: anatomic pathways of propagation. *Chest*; 73: 497–500.
- Shimizu K, *et al*. (2006). Successful video-assisted mediastinoscopic drainage of descending necrotizing mediastinitis. *Ann Thorac Surg*; 81: 2279–2281.
- Wheatley MJ, *et al*. (1990). Descending necrotizing mediastinitis: transcervical drainage is not enough. *Ann Thorac Surg*; 49: 780–784.

Pulmonary diseases in primary immunodeficiency syndromes

Federica Pulvirenti, Cinzia Milito and Isabella Quinti

Primary immunodeficiency disorders (PIDs) represent a heterogeneous group of rare immune system abnormalities, ranging from deficiencies of humoral immunity with altered B-cell and antibody production, to T-cell defects, phagocyte defects and complement deficiencies, often with a degree of overlap. Pulmonary complications of PIDs are common and contribute significantly to morbidity and mortality in these patients. Recurrent pulmonary infections, including pneumonia, lung abscess and empyema, are often the first warning sign of a PID and remain a leading cause of death from infection. As survival from infectious disease improves, noninfectious respiratory complications, (including bronchiectasis, interstitial lung disease (ILD) and pulmonary malignancy) are increasingly responsible for poor outcome in PIDs.

The risk and type of infection is dictated by the underlying defect of the immune system (table 1). Pneumonia is a common acute infection in primary antibody deficiency (PAD), which is the most commonly diagnosed PID. Studies of PAD have revealed that at least two-thirds of patients have one or more episodes of pneumonia prior to diagnosis and are prone to pneumonia-associated complications that require hospitalisation. The pathogens commonly isolated from the sputum of PAD patients are *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Streptococcus pyogenes*, with *Pseudomonas aeruginosa* and *Moraxella catarrhalis* occurring less frequently. In patients with cellular and combined immunodeficiencies and in PID patients who have undergone a haematopoietic stem cell transplant, respiratory viral infections are the major causes of morbidity and mortality. Herpes viruses, paramyxoviruses and adenoviruses are common significant pathogens in these patients. Aggressive antiviral treatments may reduce viral replication and lung damage. Failure to successfully kill organisms puts patients with phagocyte disorders at risk of necrotising pneumonias and lung abscesses *via Staphylococcus aureus* and *Klebsiella pneumoniae*. Fungal infections are typical of cellular deficiencies, and can cause morbidity and a potentially fatal outcome if misdiagnosed or incorrectly treated.

Key points

- The World Health Organization recognises >300 diseases classified as PIDs.
- The risk and type of infection changes according to the main defect of the immune system; they are classified as antibody deficiencies, combined immunodeficiencies, phagocytic disorders and innate immunity disorders.
- A PID diagnosis should be considered in patients presenting with severe and recurrent respiratory infections, granulomatous diseases or life-threatening invasive pulmonary infections.

Table 1. Microorganisms in primary immunodeficiency disorders

	Antibody deficiencies	Combined immunodeficiencies	Phagocytic defects
Viruses	Enteroviruses	CMV Respiratory syncytial virus EBV Parainfluenza virus type 3	No
Bacteria	*Streptococcus pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis* *Pseudomonas aeruginosa* *Staphylococcus aureus* *Neisseria meningitidis* *Mycoplasma pneumoniae* *Campylobacter*	As for antibody deficiencies, plus *Salmonella typhi* *Listeria monocytogenes*	*Staphylococcus aureus* *Pseudomonas aeruginosa* *Nocardia asteroides* *Salmonella typhi*
Mycobacteria	No	Nontuberculous, including BCG	Nontuberculous, BCG
Fungi	No	*Candida* *Pneumocystis jirovecii*	*Aspergillus*

CMV: cytomegalovirus; EBV: Epstein–Barr virus; BCG: bacille Calmette–Guérin. Reproduced and modified from Notarangelo (2010) with permission.

Repeated respiratory infections and sputum production are conditioning factors of permanent lung damage, leading over time to chronic obstructive disease and bronchiectasis, especially in PIDs with altered B-cell and antibody production. Severe and recurrent respiratory tract bacterial infections represent the most important morbidity and mortality factors, especially in common variable immunodeficiency (CVID), which is the most prevalent symptomatic PAD in adults (table 2).

The events that define the pathogenesis of an infection depend on a broad spectrum of variables, including the virulence of the infecting organism and the host's immunological state. IgG antibodies are only one player in a complex network of cells and mediators required to protect the respiratory tract homeostasis. The role of respiratory IgA in the immune defense against potentially pathogenic organisms is well known. The generation of secretory IgA has a basic impact on the epithelial barrier, a function that is lacking in the majority of PID patients due to a severely impaired isotype-switching process. In support of this, a very low IgA level and a decreased frequency of switched-memory B-cells represent the major independent risk factors for PAD-associated clinical conditions, as well as bronchiectasis and autoimmune disease.

Noninfectious associated respiratory diseases might also occur in PID patients and should be taken into consideration in the differential diagnosis. Obstructive airways diseases with a high exacerbation rate, including asthma, bronchiolitis and COPD, are common. An obstructive spirometry pattern is described in 33–43% of patients with PAD and is often irreversible. Bronchial wall thickening and bronchiectasis are the most common pulmonary changes observed using HCRT. Despite immunoglobulin replacement treatment, a bronchiectasis prevalence of >70% can be observed in PAD. Bronchiectasis develops due to the vicious cycle of repeated respiratory infection, airway inflammation with damaging effects and dilatation, and impaired bacterial clearance, leading in turn to recurring infection.

Table 2. European Society of Immunodeficiency registry criteria for a probable diagnosis of CVID

At least one of the following:

- Increased susceptibility to infection
- Autoimmune manifestations
- Granulomatous disease
- Unexplained polyclonal lymphoproliferation
- Affected family member with antibody deficiency
- AND marked reduction of IgG and IgA, with or without low IgM concentrations (measured at least twice; <2 SD of the normal concentration for their age)
- AND at least one of the following:
  - poor antibody response to vaccines or absent iso-haemagglutinins, or both (*i.e.* absence of protective concentrations despite vaccination)
  - low number of switched memory B-cells (<70% of age-related normal value)
  - AND secondary causes of hypogammaglobulinaemia have been excluded
  - AND diagnosis is established after the fourth year of life (but symptoms might have been present before)
  - AND no evidence of profound T-cell deficiency

Nearly 20% of PAD patients develop an ILD. Granulomatous-lymphocytic ILD (GLILD) is a unique ILD associated with CVID, and it has been reported in 8–15% of patients living with CVID. Its occurrence is indicative of a dismal prognosis, with terminal respiratory insufficiency developing in 24% of cases. It is a ‘sarcoid-like’ inflammatory process with perivascular granuloma as well as findings of nodular lymphocytic infiltrates, bronchus-associated lymphoid tissue hyperplasia, peribronchiolar lymphocytic infiltrates and lymphocytic interstitial pneumonia (LIP). GLILD is often misdiagnosed as sarcoidosis because of the presence of granulomas and a peribronchial pattern on imaging (figure 1a and b). Lung nodules >1 cm in size with random or predominantly basal distribution, bronchiectasis, hypogammaglobulinaemia and decreased circulating switched-memory B-cells could help in differential diagnosis.

The spectrum of abnormalities seen in PAD also includes cryptogenic organising pneumonia (COP), LIP and nonspecific interstitial pneumonia (NSIP). With HRCT, COP is characterised by migrating or persistent peripheral or peribronchial consolidation, whereas LIP typically presents as diffuse, bilateral ground-glass opacities, frequently in a perivascular distribution. NSIP findings include ground-glass opacities (in one-third of cases these are the only abnormalities), lobe volume loss, a reticular pattern, traction bronchiectasis, and areas of fibrosis predominantly at the basal level with a subpleural, peribronchovascular distribution (figure 1c–f).

Due to their defective immune surveillance, patients with PIDs have a five-fold greater risk of malignancy. In PIDs, lymphomas are more likely to present in extra nodal sites, including the lungs. HRCT features for pulmonary lymphoma include peribronchovascular nodules or thickening, pleural effusion, patchy ground-glass airspace opacities, mass-like consolidation (often pleural based), and hilar and mediastinal adenopathy (figure 1g and h). Bronchoscopy with transbronchial biopsy

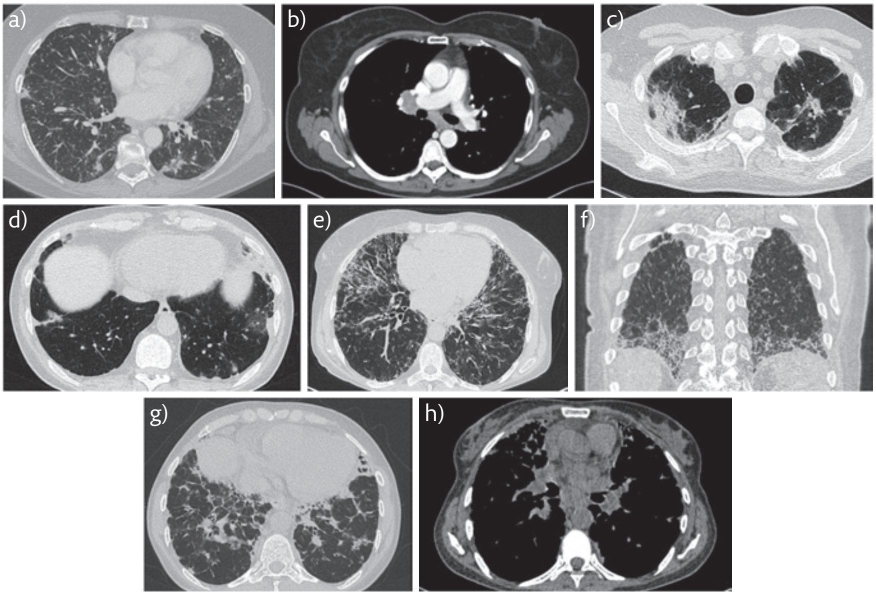


Figure 1. Noninfectious associated respiratory diseases in primary antibody disorders. a and b) Granulomatous-lymphocytic interstitial lung disease. Peribronchial and peripheral solid nodules, with initial septal reticular opacities are seen, which are more apparent in the right lung (a) associated with right hilar and subcarenal enlarged lymph nodes (b). c and d) Cryptogenic organising pneumonia; consolidations are seen in the apical and anterior segments of the upper lobe and in the apico-posterior segment of the left upper lobe (c) with ground-glass opacities and nodules in the lower left lobe (d). e and f) Nonspecific interstitial pneumonia; ground-glass opacities, thickening of the inter- and intra-lobular septa, bronchiectasis, thickening of the bronchial walls and areas of subpleural/peribronchovascular fibrosis can be seen (e); coronal image shows prevalence of peribronchial and reticular changes with increasing caudal representation (f). g and h) Bronchial-associated lymphoid tissue lymphoma; multiple pleural nodular and septal thickenings, thickened interlobular septa due to infiltration can be seen, which are associated with nodular lesions along the bronchi (g) and mediastinal lymphadenopathy (h).

and needle aspirate may confirm the suspicion *via* cytopathologic staining, flow cytometry and analysis of clonality.

HRCT plays a crucial role in the initial detection and characterisation of pulmonary changes, and in monitoring the response to therapy. Lung alterations in PID patients can also be evaluated using MRI, a radiation-free alternative to CT. Lung function tests with T_{LCO} can be useful for detecting restrictive pulmonary disease, an obstructive pattern or a pattern mix. Bronchoalveolar lavage (BAL) can be useful for identifying infectious pathogens or for excluding infections in ILDs. GLILD has been associated with BAL lymphocytosis (>20%), but whether analysis of cells retrieved at BAL means surgical biopsy can be avoided is yet to be verified. Diagnostic lung biopsy may be needed to rule out malignancy.

Treatment with antimicrobials and supplemental immunoglobulin for PIDs with defective antibody production is beneficial in reducing pneumonia and invasive infections but may be ineffective in preventing noninfectious complications. Prophylactic antibiotics, macrolides as anti-inflammatory agents, inhaled

Table 3. Clinical presentation and clinical respiratory diagnosis in PAD

Symptoms and signs	**Respiratory clinical diagnosis**
Recurrent chest infection	Bronchiectasis
Otitis media	Recurrent pneumonia
Rhinosinusitis	Asthma
Productive cough	Granulomatous lung disease
Wheeze	Hilar and/or mediastinal adenopathy
Progressive dyspnoea	Emphysema
Hypoxaemia	Previous TB
T_{LCO} alteration	Cavitating lung lesion
Polycythaemia	Rhinosinusitis
Cyanosis	COPD with recurrent exacerbation
Need for intravenous antibiotics to clear infection	

corticosteroids (ICSs), bronchodilators, mucolytic agents, and mechanical or rehabilitative respiratory methods need to be considered in the treatment of PIDs with chronic lung involvement. Treatment strategies for progressive GLILD in CVID include corticosteroids, methotrexate, azathioprine, leflunomide or mofetil mycophenolate. Recently, retrospective analyses have shown an improvement in radiographic and PFT abnormalities in CVID patients with GLILD who were treated with a combination of azathioprine and rituximab. COP typically responds well to treatment with high-dose corticosteroids followed by a slow taper. In contrast, there are few supportive data to show significant improvement in LIP with corticosteroids or other immune suppressants.

In conclusion, early recognition and diagnosis of PIDs is crucial. In pulmonology, a PID diagnosis should be considered in patients presenting with severe and recurrent respiratory infections, granulomatous diseases or with life-threatening invasive pulmonary infections (table 3). Adults with underlying structural lung damage and recurrent respiratory infections should have their baseline immunoglobulin concentrations measured at least once, including IgG, IgA and IgM, to exclude PAD. Referral to an immunologist should be sought for more specialist investigations.

Further reading

- Carsetti R, *et al.* The loss of IgM memory B cells correlates with clinical disease in common variable immunodeficiency. *J Allergy Clin Immunol* 2005; 115: 412–417.
- Nonas S. Pulmonary manifestations of primary immunodeficiency disorders. *Immunol Allergy Clin North Am* 2015; 35: 753–766.
- Notarangelo LD. Primary immunodeficiencies. *J Allergy Clin Immunol* 2010; 125: Suppl. 2, S182–S194.
- Pilette C, *et al.* Lung mucosal immunity: immunoglobulin-A revisited. *Eur Respir J* 2001; 18: 571–588.
- Plebani A, *et al.* Clinical, immunological, and molecular analysis in a large cohort of patients with X-linked agammaglobulinemia: an Italian multicenterstudy. *Clin Immunol* 2002; 104: 221–230.

- Quinti I, *et al.* Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. *J Clin Immunol* 2007; 27: 308–316.
- Quinti I, *et al.* Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: results from a multicenter prospective cohort study. *J Clin Immunol* 2011; 31: 315–322.
- Serra G, *et al.* Lung MRI as a possible alternative to CT scan for patients with primary immune deficiencies and increased radio sensitivity. *Chest* 2011; 140: 1581–1589.
- Verma N, *et al.* Lung disease in primary antibody deficiency. *Lancet Respir Med* 2015; 3: 651–660.
- Vodjgani M, *et al.* Analysis of class-switched memory B cells in patients with common variable immunodeficiency and its clinical implications. *J Investig Allergol Clin Immunol* 2007; 17: 321–328.

HIV-related disease

Marc C.I. Lipman and Robert F. Miller

HIV remains a major global public health issue. It is estimated that in 2016 there were over 36 million people living with HIV (PLHIV), 1.8 million of who were new infections. Since the start of the epidemic, around 35 million people are thought to have died. These sobering statistics are tempered by the remarkable impact of effective combination antiretroviral therapy (ART). This has transformed the lives of the estimated 57% of PLHIV who use it long term, and has led to a 50–90% fall in the incidence of many HIV-associated opportunistic infections, some malignancies, and death since the peak in 2005.

Most PLHIV experience at least one significant episode of respiratory disease during their lifetime. The associated reduction in mortality achieved by ART means that PLHIV have a life expectancy not much less than the general population. They are, therefore, now at risk of the noncommunicable pulmonary conditions that generally arise in older age. Thus, PLHIV with respiratory symptoms require careful, systematic assessment to exclude both infectious and noninfectious causes of disease.

Key points

- In populations with access to antiretroviral therapy (ART), use of combination ART has led to a marked reduction in the incidence of many HIV-associated pulmonary diseases such as *Pneumocystis* pneumonia, and improved overall outcome following a severe respiratory event.
- Despite ART, bacterial infections remain more common in people living with HIV than in the general population.
- TB may occur at any stage of HIV infection and is a common cause of HIV-related disease and death. Cases should be managed in line with appropriate public health and infection control guidance.
- In response to starting ART, there may be an overexuberant and uncontrolled immune response to exogenous antigens such as mycobacteria. This phenomenon of immune reconstitution disease can mimic a variety of other conditions and may be life threatening.
- Noninfectious respiratory complications of HIV are increasingly recognised in an ageing population. Many of these, such as COPD and lung cancer, are linked to smoking, and can run an accelerated course compared with the general population.
- Quitting smoking and immunisation are an integral component of long-term respiratory health maintenance in people living with HIV.

This chapter will focus on common causes of HIV-related respiratory illness in adults (table 1). For a given individual, the aetiology is determined by factors that include their risk of exposure to pathogens (*e.g.* through where they live or have spent time, and lifestyle, such as injecting drug use); their ability to obtain and consistently use ART successfully; the use of specific preventive therapies such as co-trimoxazole; and co-factors such as cigarette smoking. Unfortunately, there remains a large number of people who present to healthcare services with severe respiratory disease and undiagnosed HIV infection. Irrespective of whether this occurs in a high or low HIV incidence setting, this is avoidable and represents a failure of societal medical care.

In the following sections we use blood absolute CD4 counts as an indicator of HIV-related immuncompromise. This is a reasonably accurate measure of systemic and local immunity. In HIV-uninfected individuals, the CD4 count is typically >500 cells·μL^{-1}. In PLHIV with preserved immunity, typical community-acquired infections occur, although at a greater frequency than in the general population. With advancing HIV-induced immunosuppression (CD4 counts <200 cells·μL^{-1}), the risk of opportunistic infections and malignancy rapidly increases.

Infections

Bacterial infection

Prior to the use of ART, upper respiratory tract infections, acute bronchitis, and acute and symptomatic chronic sinusitis were considerably more common in PLHIV than in the general population. It is unclear if this is still the case in people using ART long term.

Table 1. Common causes of HIV-associated respiratory disease

Infectious conditions	Noninfectious conditions
Upper respiratory tract infection Acute sinusitis Chronic sinusitis Acute bronchitis Bronchiectasis	**Malignancy** Kaposi sarcoma Lymphoma Bronchial carcinoma
Bacterial pneumonia *Streptococcus pneumoniae* *Haemophilus influenzae*	**Nonmalignant conditions** COPD HIV-associated pneumonitis, *e.g.* NSIP and LIP Pulmonary arterial hypertension Pneumothorax HIV therapy causing respiratory symptoms, *e.g.* IRD
Viral infection Influenza A Rhinovirus	
TB	
Fungal infection *Pneumocystis* pneumonia *Histoplasma capsulatum* *Cryptococcus neoformans*	

NSIP: nonspecific interstitial pneumonitis; LIP: lymphocytic interstitial pneumonitis; IRD: immune reconstitution disease.

Bronchiectasis was an increasing concern in PLHIV prior to ART. This probably resulted from previous respiratory disease (such as TB, bacterial infection and recurrent *Pneumocystis jirovecii* pneumonia). In low HIV incidence, resource-rich settings, this appears to be less of a problem now, although it remains an issue elsewhere.

Compared with HIV-negative populations, bacterial pneumonia occurs six to 10 times more frequently in PLHIV not using ART. Injecting drug users are particularly vulnerable (with a risk approximately double that of other PLHIV). Other associations with bacterial pneumonia include advancing age, tobacco smoking, previous respiratory disease and advancing HIV-related immunosuppression.

The presentation of HIV-associated community-acquired bacterial pneumonia is similar to that in HIV-negative subjects. However, the chest radiograph may be atypical and mimic *P. jirovecii* pneumonia in up to half of cases. The usual pathogens isolated are *Streptococcus pneumoniae* (in up to one-third of microbiologically confirmed episodes) or *Haemophilus influenzae* (10% of cases). Infection with *Staphylococcus aureus* and Gram-negative organisms may occur in advanced HIV disease. *Mycoplasma*, *Legionella* and *Chlamydia* species are probably no more frequent in PLHIV than in HIV-negative populations.

Bacteraemia is reported to be up to 100 times more common in PLHIV with bacterial pneumonia, irrespective of blood CD4 count. These data come from studies performed prior to ART. Even so, bacteraemia is still reported in around one in six cases of bacterial pneumonia, with *S. pneumoniae* being the main pathogen implicated. This highlights the importance of performing comprehensive investigations (including blood cultures) in PLHIV presenting with community-acquired pneumonia.

Complications of bacterial infection include intrapulmonary cavitation, abscess formation and empyema. There is a high relapse rate, despite appropriate antibiotic therapy in PLHIV with advanced HIV disease. However, in most recent studies, overall mortality is similar to that in matched HIV-uninfected populations with bacterial pneumonia. Risk factors for poor outcome include advanced immunosuppression (blood CD4 $<100\ \text{cells}\cdot\mu\text{L}^{-1}$) and severe or progressive respiratory illness despite therapy.

Immunisation with pneumococcal vaccine is recommended in all adults and adolescents (at diagnosis of HIV infection and after 5 years). Conjugate vaccines, such as the 13-valent vaccine (PCV-13) appear to offer better protection than polysaccharide vaccines (*e.g.* PPV-23). Humoral responses and clinical efficacy are probably impaired in those with CD4 counts $<200\ \text{cells}\cdot\mu\text{L}^{-1}$, although vaccination can be successfully re-administered to subjects on ART who have not developed protective immunity from prior vaccination when not using ART. There remains debate whether the combination of PCV-13 and PPV-23 provides better protection than the conjugate vaccine alone, in people on long-term ART.

Viral infection

Over the last decade, the return of influenza A as a pandemic condition has served as a reminder that opportunistic viral infections, such as cytomegalovirus pneumonitis, are for many PLHIV much less of an issue than common viral pathogens. This includes rhinovirus, which appears to be frequently isolated from adults with HIV infection admitted to hospital with respiratory symptoms. In most reports, influenza H1N1 had a similar presentation and outcome in PLHIV to that seen in the general population. ART probably offers little specific protection against influenza, and annual influenza immunisation is recommended.

Fungal infection

P. jirovecii, formerly *P. carinii*, is the cause of *Pneumocystis* pneumonia (PCP). It remains a common problem in individuals unaware of their HIV serostatus, as well as among PLHIV not taking ART (with consequent blood CD4 count <100 cells·μL^{-1} and high HIV load) and/or PCP prophylaxis.

Patients present with nonproductive cough and progressive exertional breathlessness of several days' to weeks' duration, with or without fever. Examination may show features of impaired immunity such as oral *Candida* infection. However, on auscultation, the chest is usually clear, with end-inspiratory crackles audible in more severe cases. In early PCP, the chest radiograph may be normal (~10% of cases), although more frequently bilateral perihilar interstitial infiltrates are present. These may progress to diffuse alveolar shadowing over a period of days. Atypical radiographic appearances include upper zone infiltrates resembling TB, hilar/mediastinal lymphadenopathy, intrapulmonary nodules and lobar consolidation (present in up to 20% of cases). Chest CT usually confirms chest radiographic appearances, with ground-glass changes and interlobular septal thickening.

Treatment is usually started empirically in patients with typical clinical and radiological features and a CD4 count of <200 cells·μL^{-1}, pending diagnosis by cytological analysis of bronchoalveolar lavage (BAL) fluid or induced sputum samples. Recent interest in the use of molecular diagnostics for PCP has demonstrated that lung colonisation (distinct from infection and disease) is common, and that further refinements (including quantitative measures, and additional serum markers such as (1-3)-β-ᴅ-glucan, a cell wall component of many fungi) are also needed to improve the sensitivity and specificity of these tests.

PCP can be stratified clinically as mild (P_{aO_2} >11.0 kPa (>82.5 mmHg), S_{aO_2} >96% breathing air at rest), moderate (P_{aO_2} 8.0–11.0 kPa (60.0–82.5 mmHg), S_{aO_2} 91–96%) or severe (P_{aO_2} <8.0 kPa (<60.0 mmHg), S_{aO_2} <91%). This categorisation is helpful, as oral therapy may be given to those with mild disease. The first-choice treatment for PCP of all severity is high-dose co-trimoxazole (initially sulfamethoxazole 100 mg·kg^{-1}·day^{-1} with trimethoprim 20 mg·kg^{-1}·day^{-1}, reduced by 25% at day 5–7 onwards if the patient is responding to treatment) in two to four divided doses orally or intravenously for 21 days. Approximately two-thirds of patients will successfully complete this regimen. Treatment-limiting drug toxicity (*e.g.* intense gastrointestinal upset, rash, bone marrow suppression, or renal or liver dysfunction) is common, while <10% who tolerate therapy do not respond to treatment (defined by deterioration ≥5 days after initiation).

In patients with drug toxicity or poor response to co-trimoxazole, alternative therapy in mild/moderate disease includes clindamycin (450–600 mg four times daily orally or *i.v.*) plus oral primaquine (15–30 mg daily), oral dapsone (100 mg daily) with trimethoprim (20 mg·kg^{-1}·day^{-1}), or oral atovaquone suspension (750 mg twice daily). In severe disease, alternative therapy is clindamycin with primaquine or *i.v.* pentamidine (4 mg·kg^{-1} daily).

Co-trimoxazole, dapsone and primaquine should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency, and testing for the enzyme deficiency is recommended as standard practice.

Patients with an admission P_{aO_2} ≤9.3 kPa (69.8 mmHg) should also receive adjunctive glucocorticoids within 72 h of starting specific anti-PCP treatment. A frequently used regimen is prednisolone, 40 mg twice daily for 5 days, with 40 mg daily on days 6–10, and 20 mg daily on days 11–21. Adjunctive glucocorticoids have been shown to reduce the need for intensive care unit admission (and for mechanical ventilation) and mortality. Patients should be monitored carefully for steroid-related adverse events, including hypertension, hyperglycaemia, and local and systemic viral reactivation.

Several factors present on admission to hospital, or shortly thereafter, predict poor outcome from PCP. These include increasing patient age, a second or third episode of PCP, hypoxaemia, low haemoglobin, co-existent pulmonary Kaposi sarcoma and medical comorbidity. Once hospitalised, development of pneumothorax, admission to the intensive care unit and the need for mechanical ventilation are associated with a worse outcome.

Regimens for PCP prophylaxis are listed in table 2. The indications for primary and secondary prophylaxis, as well as the indications for discontinuing secondary prophylaxis, are listed in table 3. It is recommended that, if possible, all patients with an episode of PCP start ART within 2 weeks of commencing their anti-*Pneumocystis* treatment.

Tuberculosis

All patients with TB and unknown HIV status should be offered an HIV test. Active TB is estimated to occur between 20 and 40 times more frequently in PLHIV. Worldwide, >10% of new TB cases (>1000000) occur each year in PLHIV, and TB accounts for almost one in three of all HIV-related deaths. TB is also covered in other chapters, so here the focus is on issues of particular relevance to HIV co-infection.

More than two-thirds of patients with TB/HIV present with pulmonary disease. When blood CD4 counts are normal or only slightly reduced (*e.g.* >350 cells·µL^{-1}), clinical features are similar to adult post-primary disease. Chest radiography often shows

Table 2. Recommended PCP prophylaxis regimens

	Drug	Dosage	Notes
First choice	Co-trimoxazole (sulphamethoxazole + trimethoprim 5:1)	960 mg once daily[#] 480 mg once daily 960 mg thrice weekly	Protects against certain bacterial infections and reactivation of toxoplasmosis; adverse effects include nausea (40%), rash (up to 20%), bone marrow suppression (20%)
Second choice	Aerosolised pentamidine	300 mg once per month *via* jet nebuliser	Use once per fortnight if CD4 count <50 cells·µL^{-1}
	Dapsone	100 mg once daily	Plus oral pyrimethamine 25 mg once per week against reactivation of toxoplasmosis
Third choice	Atovaquone	Suspension 750 mg twice daily	
	Azithromycin	1250 mg once per week	

[#]: the use of lower doses of co-trimoxazole may be associated with fewer adverse events.

Table 3. Indications for PCP prophylaxis and its discontinuation

Indications for primary prophylaxis
Blood absolute CD4 count <200 cells·µL^{-1}
Blood CD4 count <14% of total lymphocyte count
Unexplained fever (>3 weeks' duration)
Persistent or recurrent oral/pharyngeal *Candida*
History of another AIDS-defining diagnosis, *e.g.* Kaposi sarcoma
Indication for secondary prophylaxis
All patients who have had a previous episode of PCP
Indications for discontinuing secondary prophylaxis
Patients on ART with a sustained increase in blood CD4 count (>200 cells·µL^{-1}) and undetectable plasma HIV RNA for ≥3 months (note that if CD4 count subsequently falls below 200 cells·µL^{-1} and/or the HIV RNA load increases, prophylaxis should be re-instituted)
Based on the rates of recurrent PCP noted within observational cohorts, some clinicians will discontinue treatment if the HIV load is undetectable and blood CD4 is >100 cells·µL^{-1}

upper lobe infiltrates and cavitary changes. Sputum and BAL fluid are often smear positive.

In advanced HIV disease and/or patients with a low blood CD4 count (<200 cells·µL^{-1}), the presentation is often with nonspecific malaise, fatigue, weight loss and fever. Chest radiographic abnormalities may not be specific for TB and include diffuse or miliary-type shadowing, mediastinal/hilar lymphadenopathy and pleural effusions; cavitation is uncommon. Sputum or BAL fluid is often smear negative, although culture positive. Extrapulmonary TB is common in patients with CD4 counts <100 cells·µL^{-1}. Local or disseminated infection may involve lymph nodes and bone marrow; blood cultures may be positive and it is worth obtaining specimens from as many body sites or fluids as clinically practical. For example, the yield from early-morning urine cultures is reasonable.

If smears or unspeciated mycobacterial cultures are positive, treatment should initially include a four-drug anti-TB regimen with a rifamycin (usually either rifampicin or rifabutin) plus isoniazid, pyrazinamide and ethambutol, until mycobacterial identification and drug sensitivities are known. Some clinicians will also add in a macrolide antibiotic, if there is clinical concern that the causative agent may be nontuberculous mycobacteria, such as disseminated *Mycobacterium avium-intracellulare* complex disease. It should be noted that rifamycins, in particular, can interact with components of ART, and expert advice should be sought when developing a treatment plan in PLHIV with TB, so as to avoid significant drug–drug interactions and treatment failure.

Rapid nucleic acid amplification tests are increasingly used to diagnose TB. Although less sensitive than in HIV-negative TB patients, they are superior to the older rapid test of smear and microscopy of sputum and tissue samples. As a result, they are now recommended by the World Health Organization (WHO) as a first-line test in TB/HIV endemic settings in preference to conventional microscopy and culture. The molecular probes can distinguish *Mycobacterium tuberculosis* from opportunistic mycobacteria and identify common mutations in the *rpoB* gene, which is associated with rifampicin resistance, as well as in genes associated with isoniazid resistance (*katG* and *inhA*) and with resistance to other anti-TB drugs, depending on the test kit used.

Rapid molecular diagnostic assays, such as the Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) and its new variants, are increasingly simple to use in a field/nonspecialist laboratory setting. They enable often scarce resources to be allocated effectively; for example, if a patient is shown to have rifampicin resistance using the probe, then an early decision can be made to treat for multidrug-resistant TB, and appropriate samples set up for mycobacterial culture and sensitivity testing, which may not be a part of local standard care.

Point-of-care rapid antigen assays using relatively easily obtained body fluids (*e.g.* the mycobacterial cell wall antigen lipoarabinomannan tested in urine) are of more value in PLHIV than HIV-uninfected individuals with suspected active TB. However, despite good specificity, their sensitivity means that they are of most use in patients with TB who are unwell and have advanced HIV infection (presumably due to there being a greater overall mycobacterial load).

The wider use of rapid mycobacterial detection systems has led to the discovery that ‘subclinical’ TB is common in PLHIV from TB endemic areas. Here, patients are generally well but have viable bacilli isolated from, for example, sputum and, hence, require treatment for TB. This has been reported in up to 20% of people being screened for active TB prior to starting ART. In lower TB prevalence areas, it is less common and probably occurs in, at most, 5%.

Short- and long-term response to treatment with a 6-month four-drug regimen is generally good, although patients with disseminated disease are often treated for 9–12 months. Given the reported increased risk of developing drug-resistant disease, it is recommended that PLHIV with high mycobacterial loads (*e.g.* disseminated disease, as is often present in patients with low blood CD4 counts) receive daily therapy and not higher-dose intermittent therapy (twice or thrice weekly). Compared with non-HIV-infected individuals, there is possibly a greater incidence of adverse reactions to anti-TB drugs and an increased risk of death.

ART reduces short- and long-term mortality in co-infected patients and should be started as soon as is practicable in subjects receiving treatment for active TB. Generally, the lower the blood CD4 count, the more pressing is the clinical need to start ART (*e.g.* usually within 8–12 weeks of TB diagnosis, and if blood CD4 <50 cells·μL^{-1}, within 2 weeks of starting anti-TB treatment). An important exception to this is in patients with central nervous system TB, where the risk of severe intracranial immune reconstitution disease (IRD), with associated life-threatening pressure effects, is so high when ART is started early that it should be deferred until several weeks into established anti-TB treatment, irrespective of blood CD4 count. Additional issues with early use of ART in TB patients include high pill burden, overlapping toxicities (*e.g.* neuropathy), drug–drug interactions (*e.g.* ART and rifamycins), poor adherence to complex regimens and increased risk of IRD (see later).

Multidrug- and extensively drug-resistant TB have been associated epidemiologically with HIV infection. This is probably due to the rapid development of active (and, hence, infectious) TB in PLHIV exposed to drug-resistant cases and, hence, reflects general susceptibility to developing mycobacterial disease rather than to infection with specific drug-resistant strains.

Given the high risk of latent TB infection (LTBI) progressing to active disease, the WHO recommends that PLHIV with LTBI should receive preventive treatment. As, by definition, LTBI diagnosis requires a positive immune response (*e.g.* tuberculin skin test or blood interferon-γ release assay) in an asymptomatic individual, these assessments can be affected by the immune dysregulation present in PLHIV.

Malignant conditions

Kaposi sarcoma

Kaposi sarcoma is the most common HIV-associated malignancy. Before the advent of ART, 15–20% of AIDS diagnoses were due to Kaposi sarcoma. It is associated with human herpes virus-8 (also called Kaposi sarcoma-associated virus) co-infection. Pulmonary Kaposi sarcoma is almost always accompanied by cutaneous or lymphadenopathic Kaposi sarcoma (palatal disease strongly predicts the presence of pulmonary lesions). Presentation is with nonspecific cough and progressive breathlessness; haemoptysis is uncommon.

As Kaposi sarcoma may involve both the airways and lung parenchyma, radiological findings include interstitial or nodular infiltrates and alveolar consolidation. Hilar/mediastinal lymphadenopathy occurs in ~25% of patients and up to 40% have a pleural effusion.

Diagnosis is confirmed at bronchoscopy in >50% cases by the appearance of multiple, raised or flat, red or purple endotracheal and endobronchial lesions. Biopsy is rarely performed as cutaneous Kaposi sarcoma is usually present, and diagnostic yield from biopsy is <20%. ART may induce remission of lesions and is used in addition to chemotherapy.

Lymphoma

High-grade B-cell non-Hodgkin lymphoma is the most common HIV-associated thoracic lymphoma and is usually found in association with disease elsewhere. The presenting symptoms are nonspecific. Chest radiographic abnormalities include mediastinal lymphadenopathy, pleural masses or effusions. The prognosis is considerably better if patients treated with chemotherapy also receive ART.

Bronchial carcinoma

Lung cancer is more frequently diagnosed than in the pre-ART era and is now one of the most common malignancies in PLHIV that is not AIDS-related. While in part this probably reflects the protection that ART offers from other conditions that would have occurred, the impact of high rates of tobacco smoking in PLHIV cannot be ignored. Cohort studies suggest that lung cancer risk is increased almost 20-fold in PLHIV smokers compared to nonsmokers. Lung cancer appears to be around twice as common in PLHIV than HIV-negative smokers. The clinical presentation is often late and, despite specific treatment plus the use of ART if not already prescribed, the prognosis is, therefore, often poor. Whether targeted screening programmes will improve the outlook is unclear. Thus, effective smoking cessation programmes are central to HIV-related cancer care.

Nonmalignant, noninfectious conditions

COPD

PLHIV smokers are at increased risk (by approximately 10–25%) of developing COPD, compared with HIV-negative smokers. Although this does not approach the relative risk associated with many HIV-related respiratory infections, in a similar manner to lung cancer, the onset of symptoms appears to be at a younger age and may be a more aggressive process once it starts. Some studies suggest that such individuals are more breathlessness and functionally disabled compared to HIV-negative COPD patients with equivalent lung function.

The large number of ageing PLHIV smokers, together with the synergistic effects of smoking, recurrent bacterial and opportunistic infections, injecting drug use, and possibly the direct effect of HIV in the lung (as well as the inflammatory response generated by use of ART), argue strongly for scaling up smoking cessation services. This is important, because in many settings, smoking rates in PLHIV are higher than national averages. Smoking cessation will also have an impact on other smoking-related illnesses such as cardiovascular disease and osteoporosis, which are increasingly prevalent in HIV-infected communities.

HIV-associated pneumonitis

Nonspecific pneumonitis mimics PCP but often occurs at higher blood CD4 counts. Diagnosis requires transbronchial, video-assisted thoracoscopic or open-lung biopsy. Most episodes are self-limiting, but prednisolone may be beneficial.

Lymphocytic interstitial pneumonitis is generally seen in children with HIV, and clinically resembles idiopathic pulmonary fibrosis. Diagnosis requires biopsy. Treatment with ART is often effective.

Pulmonary arterial hypertension

Pulmonary arterial hypertension is reported to be around 10 times more common in PLHIV. The presentation and management are similar to immunocompetent individuals, although use of ART is associated with improved haemodynamics and survival.

Pneumothorax

Pneumothorax occurs more frequently in PLHIV than in age-matched general medical patients. Cigarette smoking and use of nebulised pentamidine are risk factors. PCP should be excluded in any patient presenting with a pneumothorax.

HIV therapy causing respiratory symptoms

The clear beneficial impact of ART on both short- and long-term morbidity and mortality (in many cases due to its effect on reducing respiratory disease) means that starting ART immediately following HIV diagnosis or early during care is now a globally recommended standard for PLHIV. The changes in immunity that occur when ART is first started can be intense. In up to 30% of subjects who have documented or subclinical co-infection, the immune response may be overexuberant and manifest as a clinical deterioration in health status. This has been given several names, including immune reconstitution inflammatory syndrome and IRD. It has been reported to occur with many conditions, in particular mycobacterial disease and chronic fungal and viral infections.

The underlying mechanism is not completely understood, and the clinical features of IRD represent both innate and acquired host responses to exogenous antigen. The ‘paradoxical’ type of IRD is similar to that seen in non-HIV-infected patients being treated for TB, although in PLHIV it is generally more intense. Here, subjects with known TB improving on treatment start ART and within a median of 2–3 weeks develop new clinical manifestations, often at the site of their previous disease. This includes increasing peripheral lymphadenopathy, pleural or pericardial effusions or cerebral disease. There is no specific diagnostic test; therefore, drug resistance, patient non-adherence with treatment, drug–drug interactions and other disease processes occurring concurrently or *de novo* must be actively excluded. It is more common in PLHIV with low pre-treatment CD4 counts (<100 cells·μL^{-1}), faster suppression of HIV load and shorter time between starting anti-TB therapy and ART. IRD can be severe, although it is rarely fatal. When IRD is severe, it is generally due to the local pressure effects associated with a rapid increase in size of inflammatory lesions. Hence, care must be taken with IRD associated with cerebral, pericardial and, sometimes, mediastinal disease. Treatment is largely symptomatic (such as draining abscesses), although it may require glucocorticoid therapy or other inflammatory or immune modulators.

A second form of IRD is the 'unmasking' of TB. Here, a patient with latent, asymptomatic infection will rapidly develop highly inflammatory active TB at a median of 3–6 weeks after starting ART. Treatment is generally directed at the underlying mycobacterial infection. In TB-endemic areas, such as sub-Saharan Africa and South-East Asia, screening subjects for subclinical TB prior to ART initiation is important. Studies have indicated that up to one in five of individuals who are minimally symptomatic will have sputum culture-positive TB and, hence, require treatment. The use of rapid molecular and mycobacterial diagnostic tests (described earlier in this chapter) are a useful and effective means of excluding TB in people prior to starting ART.

The antiretroviral nucleoside analogue abacavir can cause a hypersensitivity reaction (in ~3% of subjects) with fever, rash and pulmonary symptoms. In these cases, recovery occurs if the drug is withdrawn. It should not be given again. Individual risk of abacavir-related hypersensitivity can be reduced by testing PLHIV prior to treatment for the presence of the major histocompatibility complex class I allele HLA-B*5701, a genetic variant that is strongly associated with drug hypersensitivity.

Further reading

- Altekruse SF, *et al.* (2018). Cancer burden attributable to cigarette smoking among HIV-infected people in North America. *AIDS*; 32: 513–521.
- Attia EF, *et al.* (2017). Bronchiectasis and other chronic lung diseases in adolescents living with HIV. *Curr Opin Infect Dis*; 30: 21–30.
- Bell L, *et al.* (2015). Paradoxical reactions and immune reconstitution inflammatory syndrome. *Int J Infect Dis*; 32: 39–45.
- Benfield T, *et al.* (2008). Second-line salvage treatment of AIDS-associated *Pneumocystis jirovecii* pneumonia: a case series and systematic review. *J Acquir Immune Defic Syndr*; 48: 63–67.
- Bigna JJ, *et al.* (2018). Prevalence of chronic obstructive pulmonary disease in the global population with HIV: a systematic review and meta-analysis. *Lancet Glob Health*; 6: e193–e202.
- British HIV Association (2018). British HIV Association guidelines for the management of tuberculosis in adults living with HIV 2018. Available from: www.bhiva.org/TB-guidelines
- Doffman SR, *et al.* (2013). Interstitial lung disease in HIV. *Clin Chest Med*; 34: 293–306.
- Fitzpatrick M, *et al.* (2013). Future directions: lung aging, inflammation, and human immunodeficiency virus. *Clin Chest Med*; 34: 325–331.
- INSIGHT START Study Group (2015). Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*; 373: 795–807.

- Lipman MCI, *et al.* (2004). An Atlas of Differential Diagnosis in HIV Disease. 2nd Edn. London, Parthenon Publishing.
- Miller RF, *et al.* (2012). Pulmonary infections in patients with human immunodeficiency virus disease. *In*: Spiro SG, *et al.*, eds. Clinical Respiratory Medicine. 4th Edn. Philadelphia, Elsevier Saunders; pp. 346–373.
- Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents (2018). Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf Date last accessed: July 18, 2018.
- Podlekareva DN, *et al.* (2016). Tuberculosis-related mortality in people living with HIV in Europe and Latin America: an international cohort study. *Lancet HIV*; 3: e120–e131.

Cardiac disease

Enrico Clini, Sara Roversi, Bianca Beghé and Leonardo M. Fabbri

Introduction, and epidemiology of concomitant lung and heart disease

The lungs and the heart are complex systems that present multiple physiological interactions, and disease of the one may influence disease of the other, particularly in chronic disorders.

Medical literature has long debated the association between lung and heart diseases, with COPD and HF, ischaemic heart disease (IHD), and arrhythmias being common topics in this field of medical research.

Accordingly, there are numerous epidemiological studies that report prevalence data on these cardiac comorbidities in patients suffering from COPD and *vice versa*. Overall, patients with COPD seem to be at higher risk of cardiac disease compared to controls (*i.e.* patients without COPD) and cardiac patients may be at higher risk of having COPD compared to controls (*i.e.* patients without heart disease), although rates vary considerably. For example, prevalence of angina and myocardial infarction in patients with diagnosed COPD ranges from 6% to 20%, due to study population, clinical setting and diagnostic criteria. A 2015 meta-analysis, trying to summarise these findings, reported that the odds of IHD was about two times higher for COPD patients compared to non-COPD (meta-OR 2.28, 95% CI 1.76–2.96, $p < 0.0001$). However, prevalence of COPD is higher in patients with cardiac disorders, although with significant rate variations among different studies. COPD has been reported in about 6–30% of patients with IHD, while 17–35% of patients with HF are estimated to have COPD, with elderly

Key points

- The literature indicates an important link between COPD, ischaemic heart disease and HF.
- The pathogenesis of the association is partially unclear but probably, recognised shared risk factors, such as smoke, altered local and systemic inflammatory response, and alteration in blood gases play a role.
- Patients with cardiorespiratory comorbidities have nonspecific symptoms and often, a correct diagnosis is challenging.
- The diagnosis of respiratory disease, as well as the treatment, should not generally deviate from international guidelines and indications, regardless of associated cardiac diseases. Similarly, cardiac diseases should be treated according to guidelines; caution may be advised for β-blockers and amiodarone.

and/or hospitalised patients usually presenting higher prevalence rates. Moreover, it has been suggested that a significant portion (*i.e.* 10–30%) of hospital admissions for HF in the USA are due to right ventricular failure and/or cor pulmonale, with the most common cause being COPD. Finally, reported prevalence rates probably underestimate the association, since a significant number of COPD patients remain undiagnosed.

Despite being the most frequently cited, COPD is not the only lung disease that has been investigated with heart disease: for example, patients with physician-diagnosed asthma seem to have a slightly elevated risk of developing atrial fibrillation compared with patients without asthma, and possibly a higher risk of cardiovascular events in general, including coronary heart disease, angina and stroke. Despite a higher prevalence of cardiovascular disease (CVD) in asthma, the association does not always reach statistical significance, and this association is generally weaker than the association between CVD and COPD. Similarly, prevalence of CVD has been reported as three to six times more common among subjects with restrictive lung function impairment compared with subjects with normal spirometry but, as with asthma, the association seems to be rather weak.

Finally, it should be noted that most pulmonary diseases may be complicated by pulmonary hypertension (PH): for example, PH in idiopathic pulmonary fibrosis (IPF) varies from 8% to 80%, and it is almost invariably associated with worsening clinical symptoms and increased mortality. With the exception of PH, which is a distinct pathophysiological disorder that complicates the majority of cardiovascular and respiratory diseases, the majority of data on lung–heart comorbidities concern the association between COPD and CVD, which will therefore constitute the main focus of this chapter.

Pathophysiology

Although epidemiology suggests a strong relationship between reduced lung function, particularly airflow limitation, and heart diseases, the pathogenesis of it remains unclear, as well as the direction of the association.

For example, IHD and COPD share common risk factors, such as smoking, advanced age and unhealthy/sedentary lifestyle. Thus, are COPD and IHD simply the consequence on the lungs and the heart of these noxious stimuli, or does one disease influence and promote the other, with a direct effect that goes beyond the common risk factors? The answer is still a matter of debate, but most authors seem to favour the second hypothesis.

Of the common risk factors, cigarette smoke is probably the most cited, with negative effects involving both local tissue damage from direct chemical exposure, and low-grade systemic inflammation and oxidative–antioxidative system imbalance. Furthermore, smoking has other pro-inflammatory actions, such as promoting the oxidation of low-density lipoprotein, enhancing platelet–monocyte aggregation and inducing overexpression of endothelial adhesion molecules. Other risk factors, such as obesity, accelerated ageing and sedentary lifestyle, have been correlated with systemic inflammation, oxidative stress and similar pro-inflammatory stimuli. Taken together, in the setting of an individual predisposition, these noxious stimuli are considered responsible for the alteration of the physiological inflammatory response, which in turn has been described as one of the major factors responsible for parenchyma destruction in COPD and coronary atherosclerosis in IHD.

Subsequently, the altered local and systemic inflammatory response has been the focus of attention when studying the relationship between COPD and IHD. Studies describing how inflammation acts in the lung and the heart are numerous. The process of disease development is complex and multifactorial, but often recognises local tissue damage as the first trigger, which in turn causes the release of numerous different cytokines and attracts inflammatory cells, promoting proteolysis, extracellular matrix degradation and fibrosis. However, when the inflammatory response is altered, its effects ultimately lead to airway remodelling and parenchyma destruction in the lung, and to endothelial damage, plaque formation and atherosclerosis in the heart. The altered inflammatory response is not limited to a single site, but is systemic, usually low-grade and chronic. This is exemplified by elevated circulating levels of markers such as white blood cells, C-reactive protein, interleukin (IL)-6 and IL-8, and fibrinogen and tumour necrosis factor α, which have been described both in IHD and COPD patients. Thus, this altered systemic inflammatory response, possibly triggered by common risk factors, is often regarded as the pathogenic link that connects IHD (and perhaps most cardiac disorders) with COPD.

Systemic inflammation may be a fundamental pathogenic mechanism, but it is not the only link between cardiac and lung diseases. For example, some data correlate reduced airflow limitation/COPD with cardiac events. In this case, it has been postulated that the alteration in blood gases, including acidosis and low oxygen, may negatively affect cardiac function and contribute to clinical manifestations such as myocardial infarction, onset of cardiac arrhythmias or acute HF. Moreover, distortions of the lung structure, emphysema and lung hyperinflation may hinder venous return due to raised intrathoracic pressure, reducing left ventricula filling and inducing ventricular dysfunction, once again promoting cardiac disorders. Accordingly, the risk of cardiovascular death and incident HF has been inversely and independently correlated with FEV_1. Similarly, having lower FEV_1 has been associated with a higher probability of developing atrial fibrillation, independent of confounding factors such as age, sex, smoking status and systemic markers of inflammation. In this regard, reduced lung function could be indicated as a risk factor for developing cardiac diseases.

Furthermore, acute worsening of COPD (*i.e.* exacerbations) has been correlated with cardiac muscle injury and increased cardiac strain, possibly due to a mixture of hypoxaemia, acidosis, reflex tachycardia, increased left ventricular afterload, infection, increased inflammatory response and enhanced oxidative stress.

To conclude, systemic inflammation is the putative pathogenic link that explains why patients with certain risk factors have a higher risk of developing both cardiac disease (especially IHD) and COPD. Other mechanisms, such as reduced lung function and altered blood gases, have been described, and are regarded as additional risk factors for the development/manifestation of cardiac diseases in the setting of lung disease.

Clinical implication and difficulties in uncovering lung disease in patients with cardiac diseases

If epidemiological data indicate a correlation between the presence of cardiac diseases and lung disease (namely COPD), and pathophysiological studies suggest that systemic inflammation and reduced lung function may be the underlying common pathogenic mechanisms, the messages deriving from clinical practice are the following:

- Patients with cardiorespiratory comorbidities have nonspecific symptoms
- In patients with known cardiovascular diseases, COPD often remains undiagnosed
- Every effort should be made for a correct diagnosis, as patients with comorbidities often fare worse

The diagnosis of COPD may present some peculiar difficulties in patients with cardiac disease. Theoretically, diagnostic criteria are well established: COPD is characterised by chronic respiratory symptoms, including dyspnoea, chronic cough and sputum production. COPD may also cause wheezing, chest tightness, fatigue and low exercise tolerance. Patients with suggestive symptoms, history of exposure to risk factors and spirometric findings indicating persistent airflow limitation should receive the diagnosis of COPD, independent of associated cardiac comorbidities. Similarly, spirometry is a useful tool in evaluating restrictive lung disorders, and thus suggests alternative diagnosis in patients with respiratory symptoms.

However, the diagnosis may not be as straightforward in clinical practice, because dyspnoea, low exercise tolerance, fatigue and chest tightness are nonspecific symptoms, which may have numerous nonpulmonary causes. For example, chronic dyspnoea is among the chief complaints of HF patients, in this case due to fluid retention and resolving with diuretic therapy. Similarly, IHD may have atypical presentation, such as worsening dyspnoea, low exercise capacity and chest tightness. Even atrial fibrillation may manifest as worsening dyspnoea and low exercise tolerance.

Therefore, the diagnosis of COPD could be overlooked at first, especially in patients at higher risk for CVD. As a result, COPD seems often to be underdiagnosed. For example, the ALICE (Airflow Limitation in Cardiac Diseases in Europe) study was a large, international, cross-sectional, observational cohort study enrolling patients with a confirmed diagnosis of IHD and a positive smoking history from cardiovascular outpatient clinics. Of the 2730 evaluable patients, 30.5% had airflow limitation and 11% had restricted spirometry. However, a previous diagnosis of COPD had been made only in 29% of patients with airflow limitation and, interestingly, in 14% of patients with restricted spirometry. This study documented not only that the lung function abnormalities were largely undiagnosed, but also that patients with both cardiac and pulmonary comorbidities had higher symptom burden and reduced health status.

A similar study aimed to determine the prevalence of airflow obstruction in stable HF, enrolling >500 consecutive stable patients from cardiac outpatient clinics and performing spirometry. Results showed that 38% of the patients had airflow obstruction. However, only 21% of them had previously been diagnosed with COPD, while 34% of the patients with a previous clinical diagnosis of COPD had no airflow obstruction (60% had normal spirometry and 40% had a restrictive pattern).

Another smaller, prospective study has investigated COPD in ~130 patients admitted to the haemodynamic unit for percutaneous coronary intervention. Spirometry was performed 1 month after the cardiac procedure and a standardised questionnaire was used to assess the previous diagnosis of COPD. According to study results, 25% of the patients met the spirometric criteria for COPD, with the majority having moderate COPD. Interestingly, the global prevalence of underdiagnosis was 82%, and while all of the severe COPD patients had been previously diagnosed, the underdiagnosis in patients with moderate and mild COPD was 89% and 100%, respectively.

The reason why COPD (and lung function alteration in general) is often misdiagnosed in patients with cardiac diseases is unknown but the nonspecific clinical presentation, especially in the setting of HF or IHD, likely plays an important role. Furthermore, spirometry is required for the diagnosis of COPD, and it should be performed only in stable and euvolaemic patients. Acute congestion and interstitial oedema influence spirometric results, as they compress and obstruct the airways, and induce bronchial hyperresponsiveness, thus leading to an overestimation of airflow obstruction. Furthermore, even stable patients with chronic lung congestion may present altered spirometry, usually exhibiting a restrictive pattern, reflecting cardiomegaly, respiratory muscle weakness and interstitial fibrosis. Therefore, in some patients with cardiac disease (especially CHF) the spirometric pattern may be mixed or difficult to interpret, and adjunctive tests with measurements of lung volumes may be necessary.

Accordingly, confirmatory tests are not often executed in hospitalised patients. For example, a retrospective study showed that spirometry was seldom performed in patients hospitalized for COPD and/or respiratory failure: among >500 patients discharged with the diagnosis of COPD, only 31% had spirometry. Moreover, ~200 patients were discharged with a concomitant diagnosis of COPD and HF, but while echocardiography was performed in 82% of them, spirometry was performed only in 36%. Lastly, spirometric findings were consistent with restrictive or normal physiology in about one third of patients with a previous diagnosis of COPD.

Nevertheless, every effort should be made to achieve a correct diagnosis, since cardiac patients with concomitant lung disease generally perform worse than patients with either lung or heart disease. Comorbid patients present worse lung function, higher pulmonary artery pressures, reduced exercise capacity and worse degree of dyspnoea. Prognosis is similarly poorer: in patients suffering from HF, COPD is an independent predictor of all-cause hospitalisation, cardiac hospitalisation, and all-cause mortality. Similarly, concurrent COPD is associated with progression of atrial fibrillation from paroxysmal to persistent, and to failure of cardioversion and catheter ablation.

Thus, it could be concluded that COPD is often underdiagnosed in patients with known cardiac disease; this is likely due to the combination of patients complaining of nonspecific symptoms, and a few difficulties in performing and interpreting confirmatory tests. However, since comorbidities significantly worsen the clinical presentation and prognosis of cardiac patients, awareness should be high and all clinicians should attempt to uncover associated lung comorbidities as a first step in planning appropriate patient management.

Minimum requirement for suspecting the diagnosis of pulmonary diseases in patients with cardiac diseases and management

The diagnosis of respiratory disease, as well as the treatment, should not generally deviate from international guidelines and indications, regardless of associated cardiac diseases. However, as stated in the previous paragraph, the presence of cardiac disease may hinder the recognition of associated pulmonary disease. Lung diseases should be considered in any patient who has dyspnoea and/or chronic cough, wheezing or sputum production, accompanied by a suitable medical history such as exposure to risk factors for the disease (*e.g.* tobacco or indoor pollution for COPD).

Although cardiac guidelines do not specifically address the diagnosis of lung diseases, the importance of differential diagnosis between cardiac and pulmonary dyspnoea is generally considered. When the symptoms are disproportionate and/or do not respond to cardiac therapy, it is necessary to search for other causes. For example, in patients with known or suspected HF, chest radiography and/or CT are of limited use in the cardiac workup, but are most useful in identifying pulmonary explanations for the patient's symptoms and signs (*e.g.* pulmonary malignancy and interstitial pulmonary disease), while pulmonary function testing with spirometry may indicate COPD or asthma (figure 1).

The second part of the figure summarises the first-line tests necessary as minimum requirements for the diagnosis of cardiac diseases and lung diseases. For example, on the left section, the ECG is the first diagnostic test when cardiac diseases are

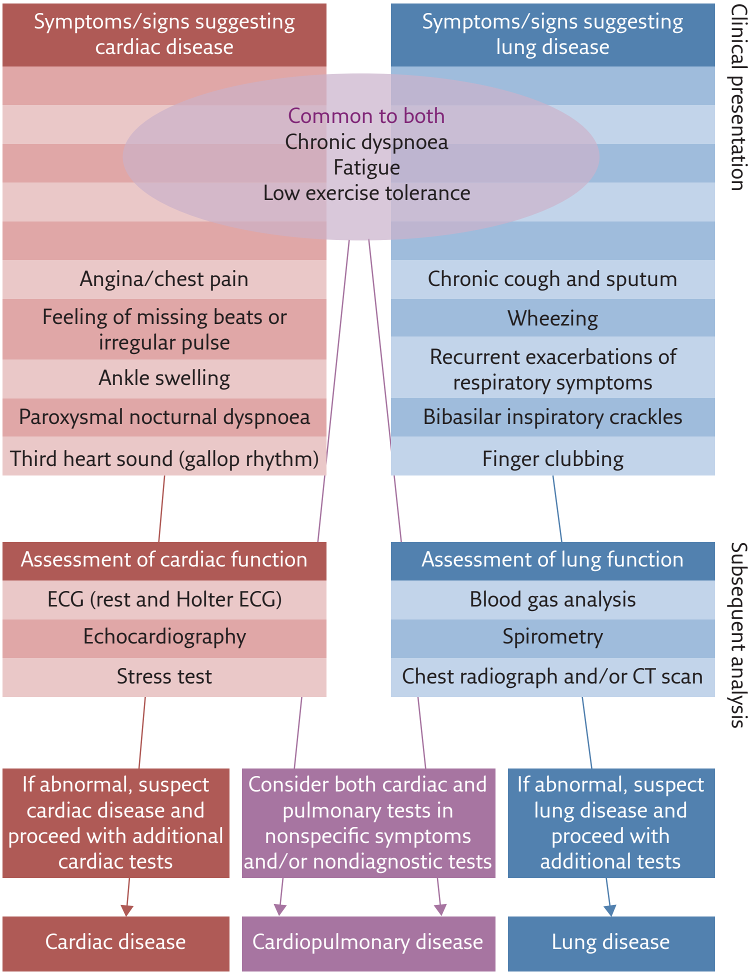

Symptoms/signs suggesting cardiac disease
Symptoms/signs suggesting lung disease
Clinical presentation
Common to both
Chronic dyspnoea
Fatigue
Low exercise tolerance
Angina/chest pain
Feeling of missing beats or irregular pulse
Ankle swelling
Paroxysmal nocturnal dyspnoea
Third heart sound (gallop rhythm)
Chronic cough and sputum
Wheezing
Recurrent exacerbations of respiratory symptoms
Bibasilar inspiratory crackles
Finger clubbing
Assessment of cardiac function
ECG (rest and Holter ECG)
Echocardiography
Stress test
Assessment of lung function
Blood gas analysis
Spirometry
Chest radiograph and/or CT scan
Subsequent analysis
If abnormal, suspect cardiac disease and proceed with additional cardiac tests
Consider both cardiac and pulmonary tests in nonspecific symptoms and/or nondiagnostic tests
If abnormal, suspect lung disease and proceed with additional tests
Cardiac disease
Cardiopulmonary disease
Lung disease

Figure 1. Schematic representation of the diagnostic flowchart in cardiac disease (red) and lung disease (blue). Cardiac and lung diseases require a careful assessment of patient symptoms and signs coupled with diagnostic tests. The top red box presents the symptoms/signs suggesting cardiac diseases and the top blue box those suggesting lung diseases; since some symptoms are common to both, they are presented in the centre (purple), and should warrant further diagnostic assessment for both cardiac and pulmonary diseases.

suspected, as it is often altered. Similarly, echocardiography is fundamental in identifying structural abnormalities such as valvular diseases, reduced left ventricular ejection fraction (suggesting HF) or regional wall motion abnormalities (suggesting previous myocardial infarction). Stress tests are useful in investigating IHD. The right section concerns lung disease. Blood gas analysis is often altered in lung diseases. Similarly, spirometry is required in certain lung diseases (*e.g.* it is necessary to make the diagnosis of COPD in the appropriate clinical context and must show a post-bronchodilator fixed ratio of FEV_1/FVC 70%), while imaging studies such as chest radiograph and CT-scans are often abnormal in patients with fibrotic lung disease and/or malignancies. Abnormal results in any of these tests should warrant for further testing as appropriate, and the final diagnosis of cardiac disease (*e.g.* HF, myocardial infarction or arrhythmias) or lung disease (*e.g.* COPD, asthma, pulmonary fibrosis) should follow recommendations from the respective international guidelines.

However, it should be noted that in some patients (purple in figure 1) symptoms are nonspecific, and therefore may warrant test for the diagnosis of both cardiac and pulmonary diseases.

Therapeutic challenges: effects of cardiac drugs on the lungs

Antithrombotic drugs, anticoagulants, statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, β-blockers and antiarrhythmic drugs are the cornerstone of therapeutic management in patients with cardiac diseases. While most of these drugs are generally well tolerated, some of them may have a negative impact on lung function.

For example, β1-receptors increase heart rate and contractility, and β1-adrenoreceptor blockade leads to left ventricular reverse remodelling, lower oxygen consumption and cardiac protection. Therefore, β-blocker drugs improve symptoms, morbidity and mortality in landmark clinical trials of HF and IHD. However, activation of β2-receptors induces relaxation of bronchial smooth muscle and bronchodilation in the lungs, and drugs that antagonise them (*i.e.* β-blockers) may provoke bronchospasm, possibly precipitating obstructive lung disease. Accordingly, asthma has long been a contraindication for β-blocker use, due to the possibility of life-threatening increase in airway resistance.

In contrast to asthma, the airflow obstruction in COPD is largely irreversible and there are no strict contraindications to β-blockers. Cardioselective β-blockers, such as bisoprolol, metoprolol succinate and nebivolol, display greater affinity for β1-receptors than for β2-receptors, likely having less effect on the airways. Therefore, selective β1-blockers are generally preferred, and current medical literature has generally reported an overall good safety profile of β-blockers in COPD. Given that β-blockers are arguably among the most powerful disease-modifying therapy in certain cardiovascular diseases, their use generally outweighs any potential risks in the general population as well as in patients with COPD.

However, evidence from several observational studies suggests that β-blockers are underused: ‘concomitant lung disease’ was one of the most powerful predictors of β-blocker underuse in past decades, with only 18% of patients with HF and COPD receiving β-blockers compared with 41% of those without COPD. Another registry showed that β-blockers were given to 84% of patients with HF, but the prevalence lowered to 73% when the patients had associated COPD. In recent years, results have been more encouraging, with only 13% of HF patients not taking β-blockers overall and only 28% of those for concomitant lung disease.

Another drug deserving mention when talking of lung disease is amiodarone. This is a potent antiarrhythmic agent, class III of the Vaughan–Williams classification, with multiple electrophysiological effects, used to treat ventricular arrhythmias and atrial fibrillation. Amiodarone has multiple side effects, including pulmonary toxicity (*i.e.* amiodarone-induced pulmonary toxicity (APT)). This drug has a complex pharmacokinetic, as it is lipid soluble and is distributed to fat and tissues, such as the lungs, thyroid, kidney and liver. Amiodarone has a long half-life (>30 days) and a slow release from the tissues, where the macrophages, including pulmonary macrophages, show a characteristic foamy appearance. The tissue accumulation reflects the sites of toxic effects, so drug sequestration and abnormal inflammatory response may be relevant determinants of toxicity. Nevertheless, the precise mechanism of tissue injury remains unknown.

Lung disease in patients treated with amiodarone was first described in the USA in the early 1980s. Later reports correlated APT with dosage, indicating higher risk with ≥400 mg·day^{-1}. Currently, APT incidence is estimated around 2–5% and is more frequent in older patients, with higher doses and longer duration of therapy. APT causes cough, progressive breathlessness and crackles on lung auscultation; occasionally, patients may be completely asymptomatic. Less commonly, patients may present with acute respiratory distress syndrome. CT generally shows diffuse ground glass and reticular abnormalities, indicating ongoing inflammatory and fibrotic changes. Pulmonary nodules or pleural effusions have also been reported. Pathological findings include interstitial pneumonitis, organising pneumonia, focal foamy alveolar macrophages or diffuse alveolar damage. None of these clinical or radiological features are specific, and other diagnoses need to be considered and excluded. In patients treated with amiodarone, periodic pulmonary follow-up has been suggested, ideally including baseline and yearly chest radiography, and pulmonary function testing. Additional testing, *e.g.* CT, bronchoscopy with bronchoalveolar lavage, or lung biopsy may be useful in selected cases. Treatment of APT consists of discontinuing amiodarone and, in severe cases, administration of corticosteroids. Although mortality may reach 10% in severely ill patients, it is substantially lower in the general population, especially if the diagnosis is made in the early stages.

To conclude, certain cardiac drugs may have direct effects on lung function or may have pulmonary toxicity. However, although some cases deserve specific attention, the final message when treating cardiac patients with concomitant lung disease remains that management of both conditions should not deviate from international guidelines.

Conclusion

Cardiac diseases may have different lung implications, with the association between CVD and COPD being the most discussed one. Published literature supports a direct correlation between COPD and IHD, HF, and arrhythmias. The mechanisms underlying this association are not clear, but likely recognise shared risk factors and abnormal systemic inflammatory responses as common causes for both lung and heart disease. Furthermore, reduced lung function might be an independent risk factor for cardiac diseases. Since the clinical presentation is dominated by nonspecific symptoms such as chronic dyspnoea, fatigue and reduced exercise tolerance, the diagnosis of COPD may be overlooked in patients suffering from cardiac diseases. However, this should be avoided, as concomitant COPD negatively affects prognosis. Patients with associated cardiac and lung comorbidities should be promptly identified and treated, to improve symptoms and outcomes. Finally, it should be noted that β-blockers and amiodarone have distinct pulmonary effects, which should be kept in mind when managing patients with cardiopulmonary comorbidities, although patient treatment should not deviate from international guidelines.

Further reading

- Chen W, *et al.* (2015). Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med*; 3: 631–639.
- Dalsgaard M, *et al.* (2017). Prevalence of airflow obstruction in patients with stable systolic heart failure. *BMC Pulm Med*; 17:(6).
- Epstein AE, *et al.* (2016). Practical management guide for clinicians who treat patients with amiodarone. *Am J Med*; 129: 468–475.

- Franssen FME, *et al.* (2016). Lung function abnormalities in smokers with ischemic heart disease. *Am J Respir Crit Care Med*; 194: 568–576.
- Li J, *et al.* (2014). Airflow obstruction, lung function, and incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*; 129: 971–980.
- MacDonald MI, *et al.* (2016). Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease. *Lancet Respir Med*; 4: 138–48.
- Roversi S, *et al.* (2016). Chronic obstructive pulmonary disease and cardiac diseases: An urgent need for integrated care. *Am J Respir Crit Care Med*; 194: 1319–1336.
- Salpeter S, *et al.* (2001). Cardioselective beta-blocker use in patients with reversible airway disease. *Cochrane Database Syst Rev*; 2: CD002992.
- Sin DD, *et al.* (2003). Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation*; 107: 1514–1519.
- Vogelmeier CF, *et al.* (2017). Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 Report: GOLD executive summary. *Eur Respir J*; 49: 1700214.

Gastrointestinal and liver disease

Harald Farnik and Gernot Rohde

Efficient transport by the oesophagus requires a coordinated, sequential motility pattern that propels food from above, and clears acid and bile reflux from below. Disruption of this highly integrated muscular motion limits delivery of food and fluid, as well as causes a bothersome sense of dysphagia, chest pain and, in some cases, aspiration (table 1).

Gastro-oesophageal reflux disease (GORD) is associated with a set of typical (oesophageal) symptoms, including heartburn, regurgitation and dysphagia. However, a diagnosis of GORD based on the presence of typical symptoms is correct in only 70% of patients. In addition to these typical symptoms, abnormal reflux can cause atypical (extraoesophageal) symptoms, such as coughing, chest pain and wheezing.

Hepatopulmonary syndrome (HPS) is defined as the presence of the triad of an arterial oxygenation defect, intrapulmonary vasodilation and the presence of liver disease. It is usually diagnosed in patients with cirrhosis, but neither cirrhosis nor portal hypertension is a prerequisite for the diagnosis, as it has been reported in chronic noncirrhotic hepatitis, noncirrhotic portal hypertension, Budd–Chiari syndrome and even in acute liver diseases, such as fulminant hepatitis A and ischaemic hepatitis.

Tracheobronchial and pulmonary lesions are relatively rare but recently, more and more frequently recognised extraintestinal manifestations of inflammatory bowel

Key points

- Oesophageal motility disorders are common gastrointestinal diseases.
- The clinical presentation is varied but classically, dysphagia, chest pain, regurgitation and aspiration are reported.
- The Chicago classification introduced new manometric parameters and better defined oesophageal motility disorders.
- Gastro-oesophageal reflux disease is the long-term, regular occurrence of acid reflux; it can cause irritating cough.
- Hepatopulmonary syndrome is characterised by the triad of abnormal arterial oxygenation caused by intrapulmonary vascular dilatations in the setting of liver disease, portal hypertension or congenital portosystemic shunts.
- Tracheobronchial and pulmonary lesions are relatively rare but recently, more and more frequently recognised extraintestinal manifestations of inflammatory bowel disease.

Table 1. Pulmonary symptoms and possible causes

Cough	GORD
Pneumonia	Achalasia
Dyspnoea	HPS
Bronchiectasis	IBD
Bronchitis, tracheobronchitis and bronchiolitis	IBD

disease (IBD). Such a possibility should always be kept in mind in the case of unusual clinical symptoms and radiological signs. The spectrum of pathological and radiological patterns is vast. First, infection, especially TB, and drug-related changes should be considered in the differential diagnosis. Greater awareness of possible pulmonary manifestations of IBD among both gastroenterologists and pulmonologists may enable better clinical vigilance.

Achalasia

Oesophageal achalasia is a primary oesophageal motility disorder characterised by the absence of oesophageal peristalsis and failure of the lower oesophageal sphincter to relax in response to swallowing. These abnormalities lead to impaired emptying of food from the oesophagus into the stomach with resulting food stasis. Most patients experience severe dysphagia and regurgitation, which can lead to aspiration and respiratory problems like pneumonia. Consequently, the quality of life of patients affected by achalasia is severely impacted. A thorough evaluation with upper endoscopy, barium swallow and oesophageal manometry is mandatory to establish the diagnosis and plan the optimal treatment. In selected patients, ambulatory pH monitoring is recommended to distinguish between GORD and achalasia.

Oesophagogastric junction outflow obstruction

Oesophagogastric junction (OGJ) outflow obstruction is a manometric diagnosis, defined as an incomplete lower oesophagus sphincter (LOS) relaxation together with intact or weak peristalsis. The symptoms most often reported are dysphagia, heartburn and retrosternal pain, the same symptoms as for which high-resolution manometry is usually performed. Botulinum toxin (botox) injections should be attempted first because of reported success in retrospective uncontrolled studies (interestingly, only a small minority of patients progresses to achalasia).

Distal oesophageal spasm

Oesophageal spasm is considered to be the consequence of impaired inhibitory innervation, and results in symptoms of dysphagia and retrosternal pain. In the latest Chicago classification (version 3.0) (figure 1), distal oesophageal spasm is defined as the occurrence of premature contractions in ≥20% of swallows in conjunction with normal OGJ relaxation. There is evidence to suggest that patients with rapid contractions without a short distal latency represent a group of patients with spastic motor disorders with a milder phenotype. Treatment should be aimed at reducing the spastic contractions in the distal oesophagus. For this purpose, calcium antagonists and nitrates have been used. Finally, peroral endoscopic myotomy (POEM) is a relatively new treatment option with a high reported success rate. Compared to botox injection, POEM has the advantage of sustained long benefit but it should be noted that this has not been tested in a randomised manner and long-term outcome data are lacking.

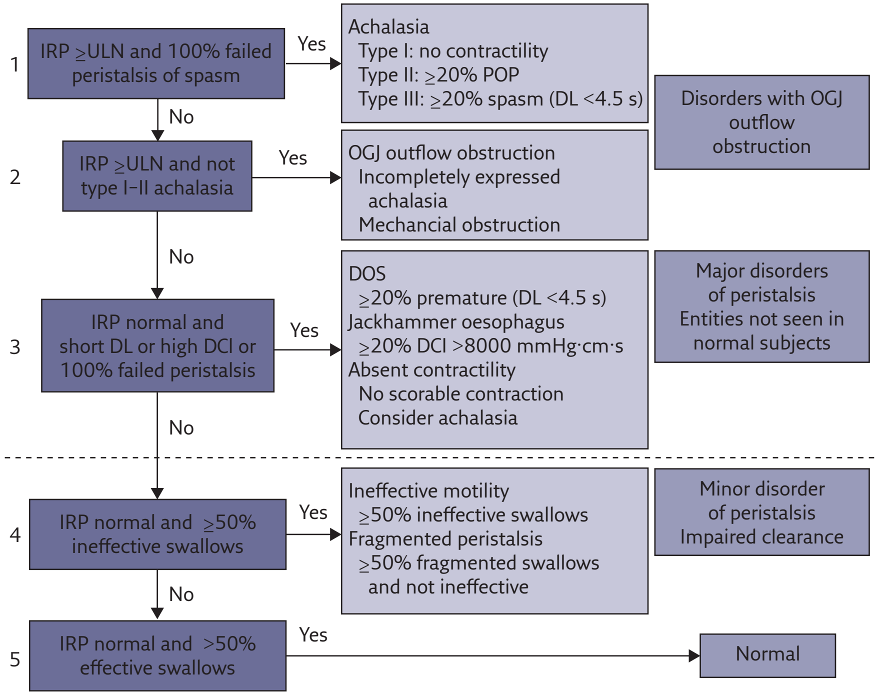

1
IRP ≥ULN and 100% failed peristalsis of spasm
Yes
Achalasia
Type I: no contractility
Type II: ≥20% POP
Type III: ≥20% spasm (DL <4.5 s)
Disorders with OGJ outflow obstruction
No
2
IRP ≥ULN and not type I–II achalasia
Yes
OGJ outflow obstruction
Incompletely expressed achalasia
Mechancial obstruction
No
3
IRP normal and short DL or high DCI or 100% failed peristalsis
Yes
DOS
≥20% premature (DL <4.5 s)
Jackhammer oesophagus
≥20% DCI >8000 mmHg·cm·s
Absent contractility
No scorable contraction
Consider achalasia
Major disorders of peristalsis
Entities not seen in normal subjects
No
4
IRP normal and ≥50% ineffective swallows
Yes
Ineffective motility
≥50% ineffective swallows
Fragmented peristalsis
≥50% fragmented swallows and not ineffective
Minor disorder of peristalsis
Impaired clearance
No
5
IRP normal and >50% effective swallows
Yes
Normal

Figure 1. Hierarchical flow chart from the Chicago classification version 3.0. IRP: integrated relaxation pressure; ULN: upper limit of normal; DL: distal latency; DCI: distal contractile integral; POP: panoesophageal pressurisation; DES: distal oesophageal spasm. Reproduced and modified from Kahrilas et al. *(2017)* Neurogastroenterol Motil *27; 160–174 with permission from the publisher.*

Jackhammer oesophagus

Jackhammer oesophagus is a hypercontractile motility disorder observed in 4.1% of patients that undergo manometry. Isolated hypercontractility following a single swallow in the oesophagus is also observed in healthy controls and is usually not associated with symptoms. Therefore, a new parameter was introduced to measure the vigour of peristalsis, the distal contractile integral (DCI). This is a multiplication of the length, duration and amplitude of contractions. Asymptomatic controls never have a DCI >8000 mmHg·cm·s and therefore, ≥20% of swallows with a DCI >8000 mmHg·cm·s is required for a diagnosis of jackhammer oesophagus. The relationship between symptoms and hypercontractility is not always straightforward. The symptom of dysphagia is accompanied with strong contractions of the LOS, signs of a possible outflow obstruction and a very high DCI. Treatment options for jackhammer oesophagus include botox injection and POEM, although data are scarce.

Absent contractility

Absent oesophageal peristalsis is not a universal finding among patients with systemic scleroderma. Absent contractility is associated with longer disease duration, interstitial lung disease, higher gastrointestinal symptom scores and impaired quality of life. The myopathy not only affects the oesophageal body but also the oesophageal sphincter, predisposing to frequent and long reflux episodes. This is reflected by the high rate of reflux symptoms (>80%), use of acid suppression (92%) and oesophagitis

(31%). Multiple rapid swallows, a simple provocation test, is abnormal in 82% of patients and could potentially be used to detect oesophageal involvement.

No pharmacological intervention can restore oesophageal peristalsis. Reflux symptoms should be treated by acid suppression, and dietary and lifestyle interventions have been proposed. Fundoplication or gastric bypass surgery is absolutely contraindicated in these patients and should be avoided.

Minor disorders of peristalsis

Ineffective oesophageal motility is diagnosed when >50% of swallows are ineffective; that is, either failed or weak. Fragmented peristalsis is defined as >50% of swallows with a large break (>5 cm) and not matching criteria for ineffective oesophageal motility. To increase clinical significance, the Chicago classification for minor disorders of peristalsis has been adjusted and several conditions that were previously seen as a disorder are now relabelled as normal.

Gastro-oesophageal reflux disease

GORD is a digestive disorder that affects the LOS. Symptoms include the taste of acid in the back of the mouth, heartburn, bad breath, chest pain, vomiting, breathing problems and wearing away of the teeth. Complications include oesophagitis, oesophageal strictures and Barrett's oesophagus.

Risk factors include obesity, pregnancy, smoking, hiatus hernia and taking certain medicines. Medications involved include antihistamines, calcium channel blockers, antidepressants and sleeping medication. Diagnosis among those who do not improve with simpler measures may involve gastroscopy, upper gastrointestinal series, oesophageal pH monitoring or oesophageal manometry. In the Western world, between 10% and 20% of the population are affected by GORD. Other causes of chest pain, such as heart disease, should be ruled out before making the diagnosis. Another kind of acid reflux, which causes respiratory and laryngeal signs and symptoms, is called laryngopharyngeal reflux or extra-oesophageal reflux disease.

Hepatopulmonary syndrome

HPS is an important cause of dyspnoea and hypoxia in the setting of liver disease, occurring in 10–30% of patients with cirrhosis. It is due to vasodilation and angiogenesis in the pulmonary vascular bed, which leads to ventilation–perfusion mismatching, diffusion limitation to oxygen exchange and arteriovenous shunting. There is evidence, primarily from animal studies, that vasodilation is mediated by a number of endogenous vasoactive molecules, including endothelin-1 and nitric oxide. In experimental HPS, liver injury stimulates release of endothelin-1 and results in increased expression of ET_B receptors on pulmonary endothelial cells, leading to upregulation of endothelial nitric oxide synthase and subsequent increased production of nitric oxide, which causes vasodilation. In addition, increased phagocytosis of bacterial endotoxin in the lung not only promotes stimulation of inducible nitric oxide synthase, which increases nitric oxide production, but also contributes to intrapulmonary accumulation of monocytes, which may stimulate angiogenesis *via* vascular endothelial growth factor pathway. Despite these insights into the pathogenesis of experimental HPS, there is no established medical therapy, and liver transplantation remains the main treatment for symptomatic HPS, although selected patients may benefit from other surgical or radiological interventions.

Because dyspnoea is common in liver disease, HPS is often missed or diagnosed late. In the absence of an alternative explanation, a saturation of <96% is suggestive of HPS. Worsening dyspnoea in the upright compared to supine position (platypnoea) and orthodeoxia (P_{aO_2} drop by >5% or 4 mmHg in the upright position) occur in only 25% of patients but are highly specific for HPS (thought to be from gravitational redistribution of blood flow to basilar parts of the lungs, where vascular dilatations are more severe), as are clubbing or cyanosis (in any patient with liver disease). Accordingly, clinicians should think of HPS in patients with liver disease and an unexplained oxygen saturation of <96%, or any of: platypnoea, orthodeoxia, clubbing or cyanosis. After pulmonary evaluation, any patient with a P_{aO_2} <80 mmHg (<10.7 kPa) or alveolar–arterial oxygen tension gradient (P_{A-aO_2}) ≥15 mmHg (2.0 kDa) that cannot be fully explained by other diagnoses should be referred for a diagnostic workup for possible HPS.

The diagnostic approach to HPS involves objective testing for each of the three components of its definition (see earleir). To begin with, evidence for liver disease is sought through abdominal imaging for liver abnormalities including cirrhosis, as well as ancillary signs of portal hypertension, such as enlarged veins (varices) and/or enlarged spleen (splenomegaly). Furthermore, blood tests that show biochemical evidence of synthetic liver dysfunction, including albumin, bilirubin and international normalised ratio, provide evidence for cirrhosis. Next, evidence for intrapulmonary vascular dilatations is sought through contrast echocardiography (or macroaggregated albumin shunt testing) and the presence of an elevated P_{A-aO_2} is determined by analysis of arterial blood gasses (ABGs). Due to the significant effect of orthodeoxia, in cases of suspected HPS, it is recommended that ABGs be performed only after 15–20 min at rest in the standing position.

Tracheobronchial involvement in IBD patients

Bronchiectasis, bronchitis, tracheobronchitis and bronchiolitis have been reported in patients with IBD. None of these complications are specific for either ulcerative colitis or Crohn's disease; however, the majority of cases concern abnormalities in the proximal or distal conducting airways in ulcerative colitis. Colobronchial and oesophagopulmonary fistulas have been reported in Crohn's disease. Symptoms of airway involvement may precede the first symptoms of bowel disease by years but most often, they appear in patients with a long history of IBD. Respiratory symptoms may accompany exacerbations of IBD but most typically, they are not parallel to exacerbations and may manifest during remissions or quiescent periods. Patients with central airway involvement usually report productive or nonproductive cough, wheezing, shortness of breath, limitations of exercise, purulent expectoration, haemoptysis, or chest pain. Asthma is frequently recognised and antiasthmatic treatment is typically started but the control of symptoms is variable.

IBD and immunosuppression

Patients with IBD, particularly those treated with immunosuppression, are at increased risk of infectious complications, especially an increased risk of pneumonia compared to the general population, with an adjusted effect estimate hazard ratio of 1.54 (95% CI 1.49–1.60). Additionally, an increased risk of pneumonia is shown among patients on corticosteroids (OR 3.62, 95% CI 3.30–3.98) and a mild to moderate increased risk in patients on anti-tumour necrosis factor agents (OR 1.28, 95% CI 1.08–1.52), but no increased risk associated with other classes of IBD medications.

Further reading

- Kahrilas PJ, *et al.* (2018). Advances in management of esophageal motility disorders. *Clin Gastroenterol Hepatol*; 18: 30385–30389.
- Lee AS, *et al.* (2018). Aspiration pneumonia and related syndromes. *Mayo Clin Proc*; 6: 752–762.
- Ott C, *et al.* (2013). Extraintestinal manifestations and complications in IBD. *Nat Rev Gastroenterol Hepatol*; 10: 585–595.
- Soulaidopoulos S, *et al*. (2018). Update on current and emergent data on hepatopulmonary syndrome. *World J Gastroenterol*; 12:1285–1298.

Haematological diseases

Anna Paola Iori

Haematological diseases are heterogeneous, including leukaemia, lymphoproliferative and plasma cell disorders, and non-neoplastic diseases (aplastic anaemia, thalassaemia and haemolytic anaemia). Pulmonary complications are common causes of morbidity and mortality in haematological diseases, and represent the most common cause for admission to the intensive care unit. Vulnerability to pulmonary complications is multifactorial: chemotherapy, immunomodulatory drugs, new targeted therapies and haematopoietic stem cell transplantation (HSCT) induce a state of profound susceptibility to infection and to lung injury.

Infectious pneumonia

Pulmonary infection is the most common complication and a primary cause of death in patients with haematological diseases despite improvements in diagnostic procedures, prophylaxis and treatment. Neutropenia, immunosuppression, hypogammaglobulinaemia, reduction of splenic function, and interruption of mucosal and cutaneous barriers, related to the underlying disease and to chemotherapeutic or immunosuppressive treatments, represent the main risk factors for the development of bacterial, fungal and viral infections. In particular, the severity and duration of neutropenia (table 1) play a major role for bacterial and fungal infections. Up to 30% of patients undergoing chemotherapy for acute leukaemia show pulmonary infection. Around 12–15% of severely neutropenic patients with first fever will present with lung infiltrates. In patients with severe neutropenia lasting for >10 days, pulmonary infections affect up to 40% of patients. Half of patients without abnormalities on chest radiography who remain febrile after ≥48 h of broad-spectrum antibacterial treatment will show lung infiltrates on pulmonary CT. Infectious complications are also frequent among patients with chronic lymphocytic leukaemia (CLL) because

Key points

- Pulmonary complications are common causes of morbidity and mortality in in patients with haematological disease.
- The severity and duration of neutropenia play a major role in pulmonary infections.
- In the era of new drugs, drug-induced pneumonia is increasing in the haematological setting.
- Patient who have undergone allogeneic haematopoietic stem cell transplantation have a high risk of developing infectious or noninfectious pulmonary complications.

Table 1. Risk of pulmonary infection according to the severity and duration of neutropenia

Grade of risk	PMNs per µL	Duration days
Low risk	500–1000	
High risk	<500	>7
	<100	<7
Very high risk	<100	>14

PMN: polymorphonuclear neutrophil.

of the complicated clinical course, which is due to complex immunodeficiency. In CLL patients treated with ibrutinib, an inhibitor of Bruton tyrosine kinase in B-cells, infectious complications occur in 56% of patients taking single-agent ibrutinib and 52% of those on combination therapy. Approximately one in five patients develops pneumonia, which is the major contributor to a 2% rate of death from infections. Many of the cases of pneumonia are due to opportunistic pathogens.

Respiratory events affect fewer than one in 10 autologous HSCT recipients. However, this proportion may be as high as 15%, particularly among patients with myeloma who experience ≥7 days of severe neutropenia, with a substantial associated mortality.

Many infectious complications have endogenous origins and derive from pathogens that normally or occasionally colonise the gastrointestinal tract. The endogenous source of infections explains the development of pneumonia and other infectious disease even if the patient is hospitalised in protected environments. However, some bacteria, such as *Pseudomonas aeruginosa* and other Gram-negative bacilli, easily spread by intrahospital contact transmission, leading to neocolonisation and, potentially, a subsequent invasive infection. Moreover, viral infections, especially herpes, which frequently occur in patients with haematological diseases, derive from endogenous reactivation. However, many infections are of exogenous origin, *via* the airways or vascular access. Environmental isolation of the patient can prevent infectious due to agents of exogenous origin (table 2).

Unfortunately, in many cases, the aetiology of pneumonia remains unknown, even if bacterial origin can be supposed both in neoplastic and non-neoplastic haematological diseases. In the last decade, many epidemiological studies have demonstrated an increased incidence of invasive fungal infections in haematological patients, due not only to the increased number of high-risk patients but also to the improved diagnostic strategies allow the identification of fungal infections, which was difficult in the past. Blood or respiratory secretion cultures, bronchoalveolar lavage (BAL) fluid cultures, and testing for the presence of galactomannan and β-ᴅ-glucan both in blood and alveolar fluid are important tools to identify the agents of the pneumonia, in order to start targeted therapy. It is interesting that chest radiography shows abnormalities in <2% of febrile neutropenic patients, who have no evident clinical signs or symptoms of lower respiratory tract infection. Among neutropenic patients with fever despite >48 h of broad-spectrum antibacterial therapy, only 10% of chest radiographs show abnormalities, while HRCT images taken at the same time show pathological findings in ~50% of patients. Hence, chest radiography is of very limited value. CT (without contrast media) must be ordered anyway as soon as possible, preferably as part of the investigation of fever during neutropenia.

Even in the setting of allogeneic HSCT, pulmonary infections represent life-threatening complications. Previous immunodeficiency, underlying haematological

Table 2. Infections due to agents of exogenous origin

Haematological disease (treatment)	Risk factors	Aetiology
Acute leukaemia (intensive chemotherapy)	PMNs <100 per µL for >14 days Extensive mucositis CVC	Bacterial pneumonia Gram-negative bacilli Gram-positive cocci Fungal pneumonia *Aspergillus* species Zygomycetes Others filamentous fungi
Acute leukaemia, myelodysplasia or aplastic anaemia (nonintensive chemotherapy)	Persistent neutropenia regardless of the degree	Bacteria pneumonia Fungal pneumonia *Aspergillus* species
Lymphoproliferative diseases (intensive chemotherapy)	PMNs <500 per µL for >7 days Prolonged steroid therapy CVC	Bacterial pneumonia T-cell defect: *Nocardia*, *Mycobacterium* B-cell defect: Encapsulated bacteria Fungal pneumonia *Aspergillus* species Interstitial pneumonia *Pneumocystis jirovecii*
Lymphoproliferative diseases (nonintensive chemotherapy)	Prolonged steroid therapy Hypogammaglobulinaemia	Bacteria pneumonia *Aspergillus* species not frequent
Autologous transplantation	PMNs <500 per µL for >7 days CVC	Bacterial pneumonia Fungal pneumonia (and sinusitis) not frequent *Aspergillus* species
Haemolytic anaemia and autoimmune thrombocytopenia	Prolonged Steroid therapy Other immunosuppressive therapy Splenectomy in some cases	Bacterial pneumonia Fungal pneumonia (and sinusitis) not frequent *Aspergillus* species Respiratory virus pneumonia

PMN: polymorphonuclear neutrophil; CVC: central venous catheter.

disease, pre-transplant conditioning regimen, type of graft *versus* host disease (GVHD) prophylaxis (*e.g.* calcineurin or mammalian target of rapamycin inhibitors), T-cell depletion, and the presence and the grade of GVHD and its treatment have been raised as the most important factors associated with an increased incidence of pneumonitis. Depending on these factors, a patient who has undergone an allogeneic transplant can be immunodeficient for months or years after HSCT, leading to a high risk of infectious complications such as pneumonitis. There is a clear relationship between the type of immunodeficiency after HSCT and the incidence of certain infections. According to this, three different phases can be distinguished after transplant, with a predominance of specific pathogens in each phase, each of them a potential cause of pneumonitis (figure 1).

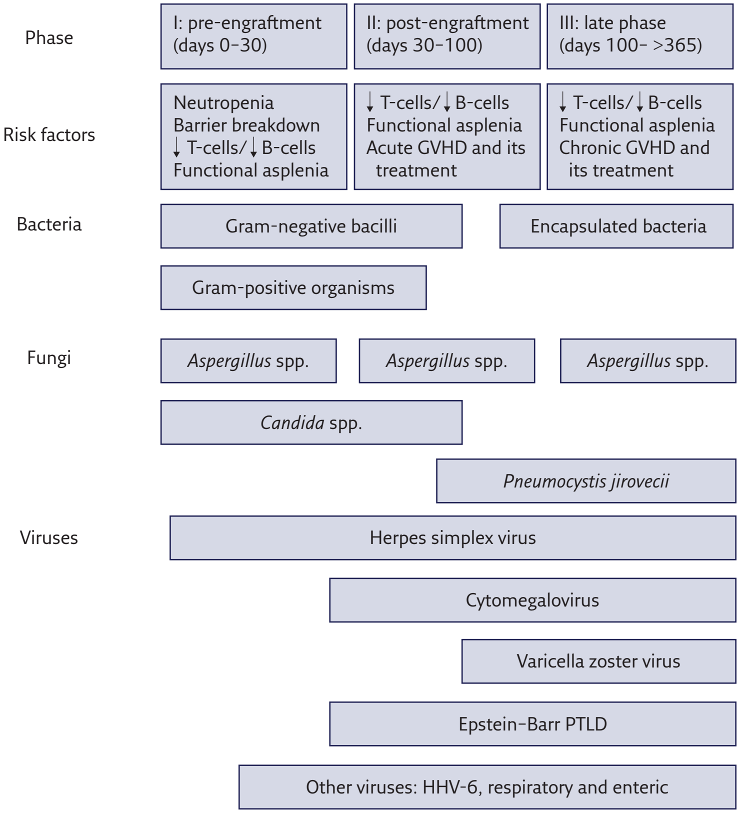

Phase
I: pre-engraftment (days 0–30)
II: post-engraftment (days 30–100)
III: late phase (days 100– >365)
Risk factors
Neutropenia
Barrier breakdown
↓ T-cells/↓ B-cells
Functional asplenia
↓ T-cells/↓ B-cells
Functional asplenia
Acute GVHD and its treatment
↓ T-cells/↓ B-cells
Functional asplenia
Chronic GVHD and its treatment
Bacteria
Gram-negative bacilli
Encapsulated bacteria
Gram-positive organisms
Fungi
Aspergillus spp.
Aspergillus spp.
Aspergillus spp.
Candida spp.
Pneumocystis jirovecii
Viruses
Herpes simplex virus
Cytomegalovirus
Varicella zoster virus
Epstein–Barr PTLD
Other viruses: HHV-6, respiratory and enteric

Figure 1. Phases post-HSCT, risk factors for infectious complications and aetiology of pneumonitis. PTLD: post-transplantation lymphoproliferative disorder; HHV: human herpesvirus.

Noninfectious pneumonia

Pulmonary haemorrhage, oedema and leukostasis are well-known noninfectious pulmonary complications in haematological patients. In the last decade, some pulmonary complications that were less common in the past have been encountered with highest frequency due to the employment of new drugs. Retinoic acid (all-*trans* retinoic acid) used in the treatment of acute promyelocytic leukaemia (APL), tyrosine kinase inhibitors used in Philadelphia chromosome positive acute or chronic leukaemias, monoclonal antibodies and other novel therapeutic strategies employed in the treatment of multiple myeloma (*e.g.* the novel proteasome inhibitor bortezomib) and CLL (*e.g.* ibritinib, an inhibitor of BCL2) can cause pulmonary complications. Therefore, it is very important that lung physicians and haematologists are aware of the possibility of drug-related lung manifestations and able to distinguish drug-induced pneumonia from other pulmonary complications. The clinical setting and radiological imaging (mainly CT) may provide clues for interpreting abnormal pulmonary opacity in patients with haematological diseases (table 3). BAL and lung biopsies (if possible) represent important tools for the diagnosis.

In the setting of allogeneic HSCT, noninfectious pulmonary complications can be observed both in the early and in the late phase after this procedure. However, the diagnosis is difficult due to overlap between the different forms of pulmonary complications.

Table 3. More common noninfectious pulmonary complications in haematological diseases

Haematological disease-related pulmonary complication	Clinical setting	CT findings
Oedema	High-volume infusions, increased permeability of pulmonary vessels, cardiotoxic effects of chemotherapy, renal impairment	Increased blood flow to the upper lobes, ground-glass opacities and consolidation, mainly distributed in perihilar or peribronchial regions with interlobular septal thickening
Leukostasis	Hyperleukocytosis (*i.e.* a white blood cell count >100 per µL), especially in the myelomonocytic subtype of acute myeloid leukaemia, due to accumulation of leukaemic cells in minor blood vessels	Nonlobular and nonsegmental ground-glass opacities caused by leukaemic cellular infiltrate in the alveolar spaces and septa, with haemorrhage and oedema from diffuse alveolar damage
	Nonspecific symptoms: cough, fever and dyspnoea	Thickening of the bronchovascular bundles and prominence of the peripheral pulmonary arteries
Haemorrhage	Thrombocytopenia, impaired coagulation or a predisposition to bleed; sudden onset of pulmonary symptoms: dyspnoea, nonproductive cough, fever and hypoxia	Widespread ground-glass opacities and consolidation, and reticulation or a crazy-paving appearance
	Haemoptysis is uncommon	
Acute lysis pneumopathy	Immediately up to onset of neutropenia post-chemotherapy	Patchy and multilobar pneumonitis
	Can be associated or not to hyperleukocytosis	
	Some extrapulmonary manifestations can be associated (*e.g.* acute tumor lysis syndrome)	

(*Continued*)

Table 3. (Continued)

Drug-induced pulmonary complications	Clinical setting	CT findings
Retinoic acid syndrome	Treatment in APL The usual manifestations include respiratory distress, unexplained fever, pleural effusion and weight gain The onset of this syndrome characteristically takes place ~10 days (range 2–21 days) after the initiation of therapy Does not typically occur in the setting of fever and severe neutropenia Fever is associated in up to 80% of patients, primarily induced by chemokines released from differentiating APL cells and is not managed with antimicrobial therapy, but glucocorticosteroids	Nonspecific findings of pulmonary oedema and/or haemorrhage An increased cardiothoracic ratio, increase in vascular pedicle width, increase in pulmonary blood volume, peribronchial cuffing, ground-glass opacities, septal lines and pleural effusion may be seen, resembling the findings in patients with pulmonary oedema due to other causes Other possible findings, including poorly defined nodules and areas of consolidation, may be due to haemorrhage from damaged endothelial cells
Tyrosine kinase inhibitor drugs	Treatment in chronic myeloid leukemia and Philadelphia-positive acute lymphoblastic leukaemia These drugs lead to various pulmonary complications, including interstitial lung disease, pleural effusion and pre-capillary pulmonary hypertension Dasatinib is the agent most frequently associated with pleural effusion, which has been reported to occur in 10–35% of patients	Homogeneous opacities with peripheral upper-lobe distribution, patchy ground-glass opacities along the bronchovascular bundle, subpleural and peribronchovascular consolidation, irregular linear or reticular opacities, and diffuse fine nodular opacities

(*Continued*)

Table 3. (Continued)

Drug-induced pulmonary complications	Clinical setting	CT findings
Idelalisib	Idelalisib is a selective, phosphatidylinositol 3-kinase δ inhibitor approved for the treatment of relapsed CLL/small lymphocytic lymphoma and relapsed follicular B-cell non-Hodgkin lymphoma By potentially interfering with the regulatory immune system, it has been associated with causing colitis, dermatitis, transaminitis and pneumonitis Cough, dyspnoea, hypoxia, interstitial infiltrates or a decline in oxygen saturation by >5% should be evaluated for pneumonitis in patients treated with idelalisib It is considered to have caused pulmonary complications in ~2% of patients who were being treated with this drug for relapsed indolent lymphoma Discontinuation of the drug and initiating high-dose corticosteroids might help to reverse this serious and sometimes fatal adverse event	Bilateral diffuse ground-glass opacities and peribronchial thickening

Pulmonary veno-occlusive disease represents sectorial endothelial damage in the context of systemic disease. Therefore, its diagnosis is very difficult and it is probably underdiagnosed.

Diffuse alveolar haemorrhage is observed in ~20% of patients who have undergone HSCT and usually occurs within the first few weeks after transplantation. The diagnosis is usually based on a finding of abnormally increased blood content (macrophages with a haemosiderin content >20%) in BAL fluid samples in the absence of signs of infection.

Engraftment syndrome is characterised by the onset of fever, erythematous skin rash and noncardiogenic pulmonary oedema during the period of engraftment following allogeneic HSCT. These clinical manifestations can be associated with increased capillary permeability. The time to onset is within 5 days of neutrophil engraftment. CT images show bilateral ground-glass opacities, areas of airspace consolidation in hilar or peribronchial regions, and smooth thickening of the interlobular septa. Corticosteroid therapy often results in rapid improvement of clinical parameters.

Late-onset noninfectious pulmonary complications involving both airways and the lung parenchyma usually appear usually between 3 months and 2 years post-transplant. However, functional consequences may persist for years. The most common delayed pulmonary complications include bronchiolitis obliterans, cryptogenic organising pneumonia (COP) and idiopathic pneumonia syndrome (IPS).

Bronchiolitis obliterans is a severe obstructive pulmonary manifestation characterised by a nonspecific inflammatory injury primarily affecting the small airways. In advanced stages, due to the progressive peribronchiolar fibrosis, restrictive functional changes develop. Bronchiolitis obliterans is considered the main pulmonary manifestation of chronic GVHD. The clinical presentation of bronchiolitis obliterans is usually insidious with dry cough, progressive dyspnoea and wheezing. In pulmonary function tests, a decline of >20% in FEV_1 from the pre-transplant value or <80% of the predicted FEV_1 should alert transplant physicians. HRCT of the chest shows a characteristic mosaic pattern. Despite immunosuppressive therapy, the mortality rate of patients with bronchiolitis obliterans can exceed 50%. In some cases, lung transplantation remains the only possible therapy.

COP is a clinical–pathological syndrome involving the bronchioles, alveolar ducts and alveoli, and presents as a restrictive respiratory complication. COP appears mainly between 1 and 12 months post-transplant with an incidence of <2%. There is a strong association between COP and GVHD. The clinical presentation is usually acute, with dry cough, dyspnoea and fever. Radiological images show peripheral patchy consolidation, ground-glass attenuation and nodular opacities.

IPS usually occurs within 120 days after transplantation and is associated with total body irradiation, GCHD and older age at HSCT. Patients conditioned with busulfan and cyclophosphamide have lower rates of IPS. Delayed-onset IPS occurring years after HSCT has been reported. HRCT shows a diffuse pulmonary parenchymal disease.

Considering the reduction in quality of life due to these complications, and the increased risk of morbidity and mortality, regular pulmonary function tests should be performed after allogeneic HSCT. If a decrease of the function tests is observed, further evaluation is warranted to start a timely immunosuppressive therapy or a pulmonary ancillary therapy. Moreover, BAL is recommended to rule out infection. The definitive diagnosis is based, when possible (bleeding risks), on histopathology.

Further reading

- Choi MH, *et al.* (2014). Acute pulmonary complications in patients with hematologic malignancies. *RadioGraphics*; 34: 1755–1768.
- Fernandez-Ruiz M, *et al.* (2018). ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Introduction). *Clin Microbiol Infect*; 24: Suppl. 2, S2–S9.
- Maschmeyer G, *et al.* (2016). How to manage lung infiltrates in adults suffering from haematological malignancies outside allogeneic haematopoietic stem cell transplantation. *Br J Haematol*; 173: 179–189.
- Rovira M, *et al.* (2019). Short- and long-term controls after HSCT. *In:* Carreras E, *et al.* eds. The EBMT Handbook. Cham, Springer Open; pp. 149–153.
- Tichelli A, *et al.* (2019). Secondary neoplasia (other than PTLPS). *In:* Carreras E, *et al.* eds. The EBMT Handbook. Cham, Springer Open; pp. 357–363.

Obesity

Frits M.E. Franssen

According to the World Health Organization (WHO), obesity is defined as excessive fat accumulation that presents a health risk. Obesity is a complex multifactorial chronic condition that develops from interaction of an individual's genotype and the environment. The interaction is characterised by long-term energy imbalance. This imbalance results from a combination of excessive calorific consumption and reduced physical activity. BMI, a person's weight (in kilogrammes) divided by the square of his or her height (in metres), of 30 or more is commonly used to classify obesity in adults. Obesity is a major risk factor for many chronic diseases. For example, obese persons are at increased risk of diabetes, cardiovascular disease, several cancers, osteoarthritis, gall stones, psychosocial problems and accidents. Also, obesity is strongly linked to respiratory physiology and diseases, as will be highlighted in this chapter.

Epidemiology

Over the last decades, the worldwide prevalence of overweight, defined as a BMI $\geq$25 kg·m^{-2}, and obesity has been rising dramatically. The WHO estimated that in 2016, more than 1.9 billion adults were overweight, of whom 650 million were obese. Thus, obesity prevalence has nearly tripled since the mid-1970s. Overall, about 13% of the world's adult population (11% of men and 15% of women) were obese in 2016. Obesity is a major contributor to global disability-adjusted life-years (DALYs) and mortality, resulting in approximately 76 million DALYs and 2.5 million deaths per year. Although initially considered a problem in high-income countries only, the prevalence of overweight and obesity is now rising tremendously in low- and middle-income countries, particularly in urban settings.

Key points

- Obesity, defined as a BMI $\geq$30 kg·m^{-2}, is strongly linked to the development, morbidity and outcome of respiratory disease, including asthma, COPD, sleep disordered breathing, respiratory infections and pulmonary hypertension.
- In adults without respiratory disease, obesity is associated with dyspnoea and limitation in physical activity, while its main effect on lung function consists of a reduced functional residual capacity.
- Management of obesity initiates with a comprehensive lifestyle intervention, consisting of dietary therapy, physical activity and behavioural modification. Additional therapies include pharmacotherapies and bariatric surgery.

Effects on lung function

In adults without obvious respiratory disease, obesity is associated with increased risk of respiratory symptoms, especially exercise-related dyspnoea, and decreased ability to perform daily physical activities. Obese persons generally breathe with lower tidal volumes and at higher rate. Ventilation is preferentially distributed to the upper zones of the lungs. Breathing discomfort during submaximal work is higher and obese adults more frequently use bronchodilators even in the absence of established airflow limitation. In order to be able to diagnose respiratory diseases in obese adults, it is essential to understand the physiological effects of obesity on lung function. Reduced functional residual capacity (FRC) is the hallmark of obesity (figure 1), with an exponential relationship between BMI and FRC. Effects on TLC and residual volume (RV) are limited. Consequently, the reduction in FRC is accompanied by an increase in inspiratory capacity (IC) and decreased expiratory reserve volume (ERV). Decreased FRC is the result of stiffening of the respiratory system in obese persons. Increased pulmonary blood flow and closure of dependent airways, resulting in micro-atelectasis, due to the mass load of adipose tissue around the rib cage and abdomen, contribute to reduced lung compliance. The effects of obesity on compliance of the chest wall *per se* are less clear, as both reduced as well as normal values have been reported.

Small reductions in FEV_1 and FVC are observed with increasing BMI and, in healthy obese persons, both are usually within the normal range. As both FEV_1 and FVC are affected to the same extent, FEV_1-to-FVC ratio is preserved or even increased in obesity. Thus, obesity has no direct effect on airflow obstruction. Expiratory flows, however, are reduced, while respiratory resistance is increased as a result of reduced lung volume and possibly airway remodelling.

T_{LCO} is normal or even increased in obese persons, the latter probably as a result of the increased blood volume. However, mild hypoxaemia and increased alveolar–arterial oxygen tension difference may occur in those with severe abdominal obesity.

Asthma

Asthma is defined as a chronic inflammatory disease of the airways, resulting in a combination of variable respiratory symptoms and airflow limitation. A relationship between asthma and obesity has been recognised for a long time. Poor dietary quality and low physical activity are common in obesity and have an impact on

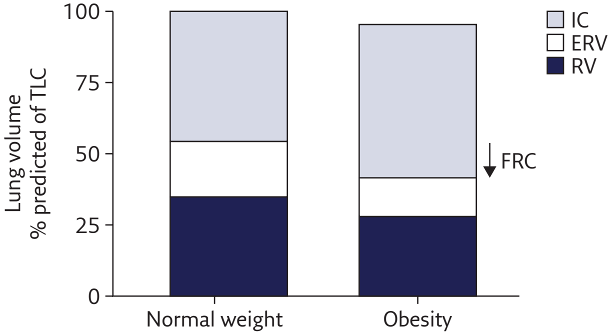


Figure 1. The impact of obesity on lung volumes. IC: inspiratory capacity; ERV: expiratory reserve volume; RV: residual volume; FRC: functional residual capacity.

asthma risk and control. Several cross-sectional and case–control studies showed increased odds of asthma in obese compared with normal BMI adults. Subsequent longitudinal cohort studies confirmed the relationship between BMI and asthma incidence, with obesity increasing asthma risk by approximately two-fold, although many studies relied on self-reported asthma diagnosis. Obese asthmatics are characterised by poor asthma control and resistance to standard controller therapies. Obesity is recognised as a contributory factor in severe asthma. Similar to asthma in non-obese patients, obesity-associated asthma is a heterogenous condition with different pathophysiological processes underlying different clinical phenotypes. Obesity-related systemic inflammatory state and increased bronchial hyperresponsiveness due to reduced lung volumes (FRC) probably account for the late-onset nonatopic obese asthma phenotype. This phenotype is more common in women than in men and is characterised by lower markers of airway eosinophilia and T-helper cell type 2 (Th2) inflammation than are typical of early-onset allergic asthma. Weight loss has beneficial effects on symptoms and exacerbations in this phenotype.

Early-onset obese asthma is another phenotype, characterised by pre-existing asthma that is complicated by obesity. It is associated with eosinophilic airway inflammation and more severe airway obstruction and airway hyperresponsiveness in comparison to normal weight asthma. Underlying mechanisms include excessive fat mass modulating the Th2 inflammatory response, glucocorticoid insensitivity and physical inactivity in obesity. Although symptoms may improve, this phenotype is less responsive to weight loss.

Chronic obstructive pulmonary disease

COPD is defined by the presence of chronic respiratory symptoms and persistent airflow limitation. Obesity is a common co-occurring condition in this disease. Indeed, several regional cohort studies reported increased prevalence of obesity in COPD compared to non-COPD. However, in a worldwide population sample adjusting for confounders for body weight, obesity was less frequent in subjects with COPD compared to subjects without chronic airflow limitation.

Misdiagnosis of COPD is more common in subjects with obesity than in those with normal BMI. Also, obese patients with a clinical diagnosis of COPD but without airflow limitation are more likely to be on inhalator therapies in comparison to normal weight patients. By treating the increased symptoms in obese adults with inhalers, healthcare professionals fail to recognise and treat alternative mechanisms of increased dyspnoea.

Lung hyperinflation, defined as an abnormal increase in the volume of air remaining in the lungs at the end of spontaneous expiration, is commonly observed in COPD and is an important cause of dyspnoea and exercise limitation. Obesity partially counteracts the effects of COPD on lung volumes, resulting in a reduction of the degree of static lung hyperinflation, irrespective of the severity of disease. Due to the beneficial effects of the excessive fat mass on dynamic ventilatory mechanics, non-weight-bearing exercise capacity (*e.g.* cycling) is preserved and dyspnoea ratings are lower in obese COPD patients compared to non-obese patients with a comparable degree of airflow limitation. However, weight-bearing exercise tolerance (*e.g.* walking) and the risk of limitations in physical activity are reduced in obese compared to non-obese patients. In patients hospitalised for acute exacerbation, overweight and obese BMI is an independent predictor of better long-term survival. Finally, in patients with severe COPD, obesity is associated with improved survival, while its contribution to the increased cardiovascular morbidity and mortality in less advanced disease remains to be established.

Respiratory infections

Adipose tissue exerts metabolic, endocrine and immunological functions. It is extensively infiltrated with immune cells, especially macrophages, and releases pro-inflammatory cytokines and adipokines. Also, lower levels of anti-inflammatory adipokines are produced in obesity. Consequently, obesity is characterised by systemic inflammation, impairing innate and adaptive immune function.

The link between obesity and infectious diseases is complex. Obese persons are more susceptible to respiratory infections and pneumonia. Increased hospitalisations, greater number of secondary infections and reduced prognosis are reported in influenza virus infection in obese persons. In addition to altered immune response, impaired glycaemic control, which is commonly present in obesity, probably contributes to these adverse outcomes. In contrast, obesity appears to be protective against mortality in bacterial pneumonia. People with a higher BMI have a reduced response to vaccinations and antimicrobial drugs.

Sleep disordered breathing

Complete or partial repetitive pharyngeal collapse during sleep defines OSA. It results in episodic oxygen desaturation, hypercapnia and sleep fragmentation, which substantially contribute to enhanced daytime sleepiness, impaired daytime function and the pathophysiology of cardiovascular and metabolic disease. OSA is a very common condition, with estimated prevalences of 25–50% in adult men and 10–25% in adult women, depending on the population sample and diagnostic techniques and criteria used. In addition to male sex and advancing age, obesity is consistently recognised as the major risk factor for OSA; almost half of all OSA patients are obese. Accumulation of fat around the upper airway with increasing BMI results in increased extraluminal pressure and decreased pharyngeal airway lumen, leading to enhanced risk of upper airway collapse, especially during rapid eye movement (REM) sleep. Other factors, including stability of the respiratory control system, reduced chest wall compliance in obesity and low arousal from sleep threshold, also contribute to pathophysiology of OSA. CPAP is the initial therapy for patients with OSA and improves not only patient-reported outcomes but also intermediate cardiovascular outcomes. However, a role for positive airway pressure therapies for reducing cardiovascular mortality has not been demonstrated. CPAP therapy must be combined with education on risk factors, natural history and adverse health consequences of OSA, and behavioural modification. Especially, weight loss should be stimulated (see section on management of obesity).

Obesity, particularly when severe (BMI $\geq$40 kg·m^{-2}), carries a risk for concomitant obesity hypoventilation syndrome (OHS), defined as the development of diurnal hypercapnia in obese persons in the absence of other reasons for hypoventilation. The prevalence of daytime hypercapnia in persons attending sleep clinics varies between 10% and 40%. Restrictive lung function impairment contributing to ventilation inhomogeneity, increased work of breathing, respiratory muscle dysfunction and abnormal ventilatory control are additional factors that contribute to worsened gas exchange in OHS. Patients with OHS are at increased risk for pulmonary hypertension and cardiovascular morbidity and mortality. OHS is an indication for NIV, both CPAP as well as bilevel positive airway pressure (BiPAP) and results in clinical and psychosocial improvement.

Pulmonary hypertension

Pulmonary hypertension, defined by an increased mean pulmonary artery pressure, is a potentially life-threatening condition arising from variation of pathophysiological mechanisms. The link between pulmonary hypertension and obesity is multifactorial. Repetitive chronic upper airway collapse and oxygen desaturation in OSA and/or OHS can lead to hypoxic pulmonary vasoconstriction and contribute to pulmonary hypertension and right ventricular failure. Indeed, it is known that 5% of normal obese persons have pulmonary arterial systolic pressure >50 mmHg, with higher percentages reported in patients with OSA. The role of isolated obesity in pulmonary hypertension remains unclear. CPAP treatment results in lowering of pulmonary pressures. In the past, use of (met) amphetamine analogues to support weight loss was strongly linked to the (nonreversible) development of primary pulmonary hypertension. In extreme obesity, myocardial steatosis and increased volume load on the left ventricle may develop and lead to cardiomyopathy of obesity. This is characterised by eccentric ventricular hypertrophy and diastolic heart failure. The syndrome is associated with left ventricular failure and can lead to secondary pulmonary hypertension. Weight loss will improve cardiac function in this condition.

Obesity is an independent risk factor for thromboembolic disease; sedentary lifestyle, systemic inflammation and insulin resistance in obesity are additional factors associated with occurrence of venous thrombi.

Management of obesity

Comprehensive lifestyle interventions are the first step in the treatment of obesity. These include dietary therapy, physical activity and/or behavioural modification. Dietary therapy should involve reducing calorific intake to create an energy deficit of 500–1000 $\mathrm{kcal \cdot day^{-1}}$ and education on how to modify the diet to achieve this goal. While most weight loss occurs because of decreased calorific intake, increased physical activity can contribute to creating a negative energy balance by increasing energy expenditure. Also, physical activity may contribute to improving body composition by reducing body fat and preventing a decline in muscle mass that is often found during weight loss. In addition, it increases cardiorespiratory fitness and reduces cardiometabolic risk beyond that produced by weight loss. Physical activity should be performed for ~30 min or more, 5–7 days per week, to prevent weight gain and to improve cardiovascular health. Behaviour therapy, such as development of self-monitoring strategies, should be included in order to improve compliance to scheduled adjustments in food intake and physical activity. For patients who have not met the weight-loss goals of a comprehensive lifestyle intervention, several pharmacological therapies are available, the choice of which depends on the comorbidities and relative contraindications present in the individual patient. Bariatric surgery is an additional treatment option for adults with a BMI $\geq 40\ \mathrm{kg \cdot m^{-2}}$, or a BMI of 35–39.9 $\mathrm{kg \cdot m^{-2}}$ with at least one serious comorbidity, who have not met weight-loss goals with diet, exercise and drug therapy. In order to prevent regaining of lost weight, frequent self-weighing, reduced-calorific diet and high levels of physical activity are recommended.

Pulmonary rehabilitation comprises an evidence-based, personalised and comprehensive nonpharmacological intervention for symptomatic patients with chronic respiratory disease. While the combination of exercise training and education is considered the cornerstone of pulmonary rehabilitation, nutritional counselling is another important intervention during pulmonary rehabilitation programmes. Hence, pulmonary rehabilitation offers the opportunity for effective obesity management in patients with respiratory diseases.

In obese asthmatics, hypocalorific diet counselling sessions combined with behavioural techniques and exercise training results in improved clinical control, greater weight loss and enhanced aerobic capacity compared to a weight-loss programme only. Improvements in airway and systemic inflammation following exercise training in asthma are also well recognised.

Patients with OSA should be recommended to lose weight and engage in exercise. Although it rarely leads to remission of OSA, weight loss lowers the severity of OSA. Also, it improves health status and metabolic outcomes, reduces blood pressure and decreases daytime sleepiness. Exercise may modestly improve OSA even in the absence of significant weight loss.

Further reading

- Dhurandhar NV, *et al.* (2015). Interaction of obesity and infections. *Obes Rev*; 16: 1017–1029.
- Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults (1998). Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. *Am J Clin Nutr*; 68: 899–917.
- Franssen FM, *et al.* (2008). Obesity and the lung: 5. Obesity and COPD. *Thorax*; 63: 1110–1117.
- Friedman SE, *et al.* (2012). Obesity and pulmonary hypertension: a review of pathophysiologic mechanisms. *J Obes*; 2012: 505274.
- Jordan AS, *et al.* (2014). Adult obstructive sleep apnoea. *Lancet*; 383: 736–747.
- Jubber AS (2004). Respiratory complications of obesity. *Int J Clin Pract*; 58: 573–580.
- Mancuso P (2013). Obesity and respiratory infections: does excess adiposity weigh down host defense? *Pulm Pharmacol Ther*; 26: 412–419.
- Nie W, *et al.* (2014). Obesity survival paradox in pneumonia: a meta-analysis. *BMC Med*; 12: 61.
- Salome CM, *et al.* (2010). Physiology of obesity and effects on lung function. *J Appl Physiol*; 108: 206–211.
- Sin DD, *et al.* (2008). Obesity and the lung: 4. Obesity and asthma. *Thorax*; 63: 1018–1023.
- Vanfleteren LE, *et al.* (2016). Body mass index and chronic airflow limitation in a worldwide population-based study. *Chron Respir Dis*; 13: 90–101.
- World Health Organization. Health topics: Obesity. www.who.int/topics/obesity/en/ Date last accessed: January 17, 2019.

Connective tissue diseases

Edoardo Rosato

Connective tissue diseases (CTDs) are autoimmune diseases characterised by the involvement of several organs and the presence of autoantibodies. These immune-mediated disorders characteristically involve inflammation, tissue damage and fibrosis with loss of function of the target organ. The pathogenesis of CTDs, although multifactorial, is not well known; nevertheless, some of the autoantibodies are directly involved in tissue damage, whereas some are just markers of disease development. The main diseases are systemic sclerosis (SSc), mixed connective tissue disease (MCTD), polymyositis/dermatomyositis (PM/DM), systemic lupus erythematosus (SLE), Sjögren syndrome (SS) and rheumatoid arthritis (RA). Numerous comorbidities are associated with CTDs such as atherosclerosis, cardiovascular disease, infections and complications resulting from treatment. The lung is a frequent target of autoimmune-mediated injury in patients with CTDs and pulmonary involvement is a leading cause of morbidity and mortality.

Epidemiology

SSc affects female adults (the female:male ratio is 7:1) of all ages with a peak age of onset between 40 and 50 years of age. The prevalence is estimated at about one in 6500 adults. Raynaud's phenomenon and digital ulcers are the main features of the disease (figure 1). MCTD appears to have a prevalence of approximately four cases per 100000 persons, with a female predominance and a peak age of onset between 30 and 40 years of age. The prevalence of PM/DM is approximately one case per 100000 persons. These diseases, which are twice as common in females, can occur at any age but have a bimodal incidence pattern with a first peak in childhood (10–15 years of age) and a second between 35 and 65 years of age. SLE has a prevalence of 15–124 cases per 100000 of the population worldwide and occurs predominantly in women of childbearing age (the female:male ratio is 6:1). Primary SS affects women (the female:male ratio is 9:1) in their fourth to fifth decade with an estimated prevalence between 0.5% and 1%. RA affects approximately 1% of the population worldwide, and women are twice as likely as men to be affected. RA can occur in individuals of any age with the peak incidence between the fourth and sixth decade.

Key points

- Lung involvement is a major determinant of morbidity and mortality in connective tissue diseases.
- All structures of the lung can be involved in connective tissue diseases.
- Interstitial lung disease and pulmonary arterial hypertension are the most important manifestations of lung involvement.

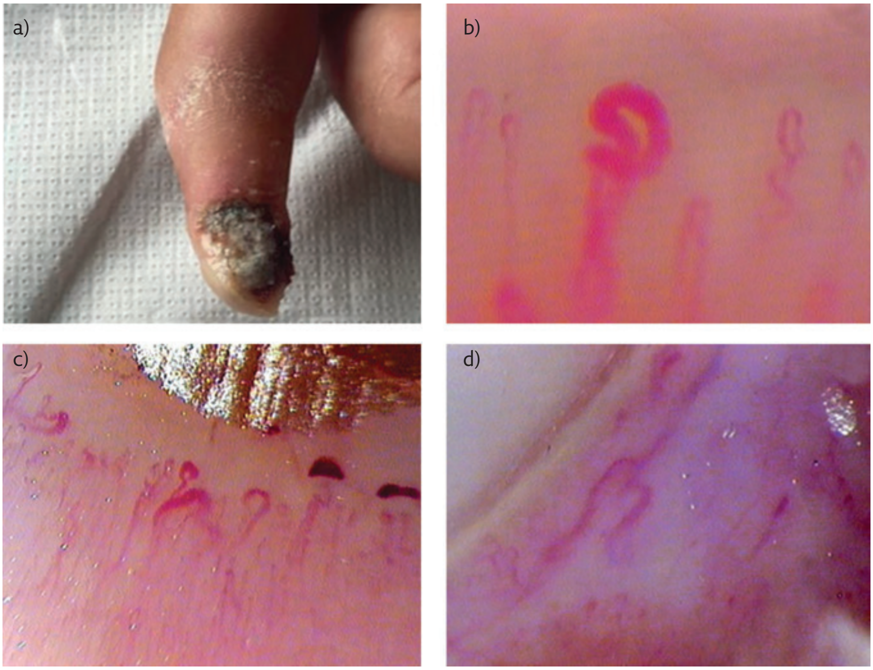


Figure 1. Digital involvement in SSc. a) A digital ulcer on the fingertip. The nailfold videocapillaroscopy showed b) giant capillaries, c) giant capillaries and haemorrhages, and d) loss of capillaries and disorganisation of the microvascular array.

Clinical features

Lung involvement is a major determinant of morbidity and mortality in CTD patients. Lung involvement is very heterogeneous and all lung structures may be targets for immune-mediated damage. In CTDs, primary pulmonary disease is represented by lung parenchyma involvement and pulmonary hypertension (PH).

Interstitial lung disease (ILD) is the most common lung involvement in SSc, MTCD and PM/DM (up to 70–90% of patients). By contrast, in RA and SLE the spectrum is very large and all lung structures may be affected by immune-mediated damage. Furthermore, the clinical manifestation and severity of lung disease varies from subclinical abnormality to respiratory failure.

The histopathological classification of ILD associated with CTDs follows the 2013 revised American Thoracic Society/European Respiratory Society classification of idiopathic interstitial pneumonia, including usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP) (figure 2), cryptogenic organising pneumonia (COP) and diffuse alveolar haemorrhage (DAH). Dyspnoea during exercise is the most common symptom, which is followed by cough. The most common pattern of ILD in SSc, MCTD and PM/DM is NSIP. In RA, ILD is present about 10% of patients and UIP and COP are the most common patterns.

Pulmonary arterial hypertension (PAH) is very common in patients with SSc and MCTD (up to 7–12% of patients). The pathogenic mechanisms underlying PAH are abnormal proliferation, vasoconstriction and thrombosis of the pulmonary vasculature. The presence of PAH is defined at right heart catheterisation (RHC) by a mean pulmonary

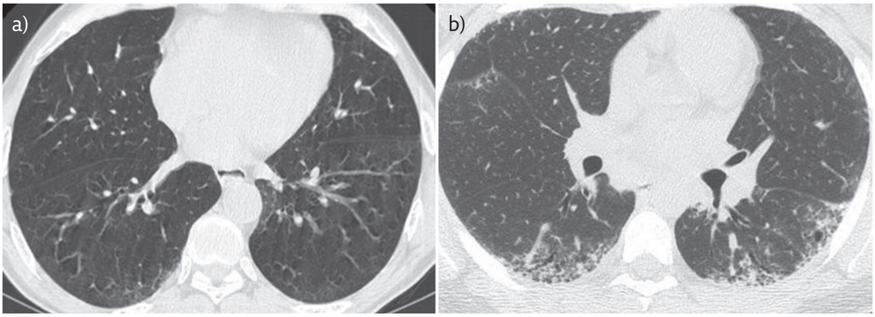


Figure 2. NSIP in SSc. CT images showing a) ground-glass; and b) honeycomb patterns.

arterial pressure of ≥25 mmHg (≥3.33 kPa) with a pulmonary capillary wedge pressure of ≤15 mmHg (≤2.00 kPa). In SSc, PH from left heart dysfunction and PH secondary to ILD can be observed. In PM/DM, PH is often secondary to ILD and isolated PAH is rarely found. The prevalence of PAH in SLE is typically around 4–5%. Anti-cardiolipin antibodies, Raynaud's phenomenon or anti-U1 RNP antibodies were found to associate with PAH in SLE.

Airway diseases and pulmonary nodules are often observed in CTDs. Airway involvement is present in 39–60% of RA patients. Both upper and lower airways can be involved. The most common form of upper airway involvement is cricoarytenoid arthritis, while bronchiectasis, bronchiolitis with air trapping and bronchial wall thickening are the most frequent manifestations of lower airway diseases. Airway involvement is present in 9–24% of SS patients. Lesions affecting the small airways, such as follicular bronchiolitis, are among the most common histological findings in SS patients with pulmonary involvement. COPD is present in 30% of SS patients. SS patients develop lymphoproliferative disorders with a high frequency. Bronchus-associated lymphoid tissue (BALT) lymphoma is frequently observed in SS patients.

Pleural manifestations (pleuritis, pleural effusion, pleural nodules and pleural fibrosis) are most common in SLE and in RA. Pleural involvement constitutes one of the classification criteria for SLE and it has been observed in up to 50% of SLE patients. Effusions are either bilateral or unilateral. The pleural fluids in lupus pleuritis are often exudative, with increased leukocyte cell count. Pleural abnormalities associated with RA include pleural effusion, pleuritis, pleural nodule, pneumothorax and fibrothorax.

Secondary pulmonary disease is due to broncho-aspiration (*e.g.* secondary to gastro-oesophageal reflux or toxicity due to medications and infections). Table 1 shows the patterns of involvement in CTDs.

Investigations including radiology and severity assessment

Interstitial lung disease

The physical examination can be normal or fine crackles can be found in the lower lobes; however, in patients with cor pulmonale the symptoms and signs of heart failure are present. The gold standard for diagnosing of ILD is pulmonary biopsy. HRCT has a sensitivity of 90–100% for the detection of parenchymal disease in these patients. HRCT is useful not only to evaluate the extent of disease but also to evaluate the response to treatment. T_{LCO} and pulmonary function tests (PFTs) with evaluation FVC and TLC showed a low sensitivity but high specificity. T_{LCO} and PFTs are useful for screening and to evaluate the response to therapy. Lung ultrasound has a high

Table 1. The common manifestations of lung involvement in CTDs

Manifestation	SSc	MCTD	PM/DM	SLE	SS	RA
ILDs						
NSIP	+++	++	+++	+	+	+
UIP	+	+	+	+	+	++
COP	+	+	++	–	–	++
DAH	–	–	–	++	–	–
PAH	+++	++	–	+	–	–
Pleural disease	–	+	–	+++	–	++
Airway disease	–	+	–	+	++	++
Aspiration pneumonia	+++	+	+	–	–	–
Respiratory muscle dysfunction	–	+	++	+	–	–
Parenchymal nodules	–	–	–	–	–	+

The symbols indicate the prevalence of lung manifestations. –: absent; +: low prevalence; ++: medium prevalence; +++: high prevalence.

diagnostic accuracy and plays an important role in the diagnosis and follow-up of CTD. The presence of B-lines correlates with HRCT score.

Pulmonary arterial hypertension

In PH/PAH associated with CTD, PFTs especially changes in *T*LCO, circulating biomarkers (N-terminal pro-brain natriuretic peptide) and echocardiography have long been used as screening tools. RHC represents the gold standard for diagnosing of CTD-PAH. In SSc-PAH, the DETECT study proposed a multistep approach to diagnosis of PAH. A stepwise detection approach was proposed with six simple clinical and biological assessments in step 1 of the algorithm determining referral to echocardiography. In step 2, the step 1 prediction score and two echocardiographic variables determined referral to RHC.

Differential diagnosis

The differential diagnosis includes idiopathic pulmonary fibrosis (IPF), idiopathic interstitial pneumonias, chronic hypersensitivity pneumonitis, sarcoidosis, COPD and all forms of group 1 PAH according to the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines for the diagnosis and treatment of PH.

Management

The treatment for ILD is quite empirical, because there have been no randomised placebo-controlled trials. Common immunosuppressants, such as azathioprine, cyclophosphamide or mycophenolate mofetil, alone or in combination with steroids have been used. In SSc patients, the EULAR recommendation still suggests cyclophosphamide preferentially over mycophenolate mofetil.

Systemic prostacyclin analogues, endothelin-1 receptor antagonists and phosphodiesterase type 5 inhibitors have been used to treat PAH according to the 2015 ESC/ERS guidelines for the diagnosis and treatment of PH.

Further reading

- Jameson JL, *et al.* (2018). Harrison's Principles of Internal Medicine. New York, McGraw-Hill Education.
- Paschalaki KE, *et al.* (2016). Monitoring of lung involvement in rheumatologic disease. *Respiration*; 91: 89–98.
- Robles-Perez A, *et al.* (2015). Treatment considerations of lung involvement in rheumatologic disease. *Respiration*; 90: 265–274.
- Sambataro G, *et al.* (2018). State of the art in interstitial pneumonia with autoimmune features: a systematic review on retrospective studies and suggestions for further advances. *Eur Respir Rev*; 27: 170139.

Cystic fibrosis

Marcello Di Paolo, Joseph Stuart Elborn, Francesco Blasi and Paolo Palange

Pathophysiology of CF

CF is the most common life-limiting autosomal recessive genetic disorder among Caucasians, with the highest prevalence in Europe, North America and Australia. Although commonest in white people, it has been found in virtually every ethnic group. The responsible gene, located on the long arm of chromosome 7, encodes a multifunctional protein called the cystic fibrosis transmembrane conductance regulator (CFTR), which is active at the apical membrane of epithelial cells in several human body systems. CFTR functions as a chloride channel, but also regulates

Key points

- CF is common in Europe, with patients surviving into middle age and beyond, and new diagnoses of CF are even being made among adult individuals. Due to more widespread national newborn screening programmes and the remarkable improvement in CF care, a progressively larger number of fitter patients will be transferred to adult clinics over the next decades.
- CF is a multisystem disease. With ageing, complications, such as cirrhosis and liver failure, diabetes, osteoporosis, infertility, stress incontinence and depression, become more common and relevant to the patients, in addition to the classical signs of the disease (*i.e.* chronic respiratory infections, irreversible lung disease and malnutrition).
- With increased survival and exposure to multiple antibiotics, infections from multidrug-resistant strains and atypical pathogens are becoming more common.
- Treatment of adult CF is challenging and the presence of a dedicated multidisciplinary team with proper age-specific expertise is key to improving clinical outcomes.
- Increasing knowledge of the molecular pathophysiology of CF is leading the way for development of CFTR-targeted therapies (so-called ‘modulators’), which now cover a large portion of potential candidates.
- Lung transplantation remains the main therapeutic option for end-stage pulmonary disease. Referral to transplant team must be considered as early as possible when signs of poorly controlled disease become evident.
- In countries where provision of care in adult centres is underrepresented there is an urgent need for more adult pulmonologists to be trained in CF care and appropriate provision made for effective transition from paediatric care.

bicarbonate cross-membrane transport as well as the activity of other ion channels, with well-known effects on the epithelial sodium channel (ENaC).

The phenotypic expression of the disease varies widely and is influenced by genotype, modifier genes and environmental exposure. After identification of the gene in 1989, more than 2000 different variants have been detected, many of which are recognised as of unknown clinical relevance or definitely not associated with development of CF. The most common allele worldwide is p.Phe508del. Different classes of CFTR gene mutations have been classically described according to their effects on protein structure and function (figure 1). The lower the preserved CFTR channel function the higher the severity of disease; therefore, mutations in classes I to III tend to cause more severe disease than those in classes IV to VI. However, the clinical implications of a specific combination of mutations are often unclear, perhaps because of the influence of gene modifiers. Genotype–phenotype correlations are weak for pulmonary disease in CF and somewhat stronger for pancreatic exocrine function. The links between genetic and phenotypic information are collected by an international consortium called "Clinical and Functional Translation of CFTR" and results are regularly updated and made available on the consortium's website (www.cftr2.org).

The most popular hypothesis for the pathophysiology of CF lung disease is airway surface liquid dehydration due to uncontrolled activity of ENaC secondary to CFTR dysfunction. In addition, further models have been proposed to explain other classical features of CF such as susceptibility to chronic airway infections from multiple pathogens, impaired innate immunity and abnormally raised inflammation, which are thought to be responsible for airway remodelling since prenatal age.

Median survival for current CF newborns is predicted to be ~50 years, longer for males. Thus, the clinical management of CF no longer has a paediatric predominance. In many countries, children account for less than half of the CF population, with the focus and burden of care gradually shifting towards adult care centres. Most of the morbidity and mortality of CF patients is due to chronic airway infection leading to irreversible end-stage respiratory failure, but as adults survive longer, multisystem complications, such as liver disease, diabetes, osteoporosis and depression are becoming more important.

Adult physicians will encounter CF patients by two routes:

1) Referral of a patient from a paediatric clinic. Transition from the paediatric to adult clinic should be managed by well-defined transitional strategies and needs to be handled with sensitivity by competent staff. This should usually involve adult teams liaising closely with their paediatric counterparts. Optimum transition is managed through joint clinics during the teenage years.
2) A new diagnosis made in adult life: although CF is usually diagnosed in early childhood, by newborn screening, mild atypical cases may be missed. In some European countries up to ~15% of cases are diagnosed during adult life (table 1). The diagnosis should be considered even in people born in areas where CF newborn screening is offered. Children with residual function mutations may give false negative results in screening tests (*e.g.* blood spot immunoreactive trypsinogen), or the patient may have moved from an area where screening is not offered.

Diagnosis

Diagnosis is based upon compatible clinical findings with functional or genetic confirmation. The sweat chloride test is the mainstay of laboratory confirmation. Both clinical and functional criteria must be met to diagnose CF (table 2).

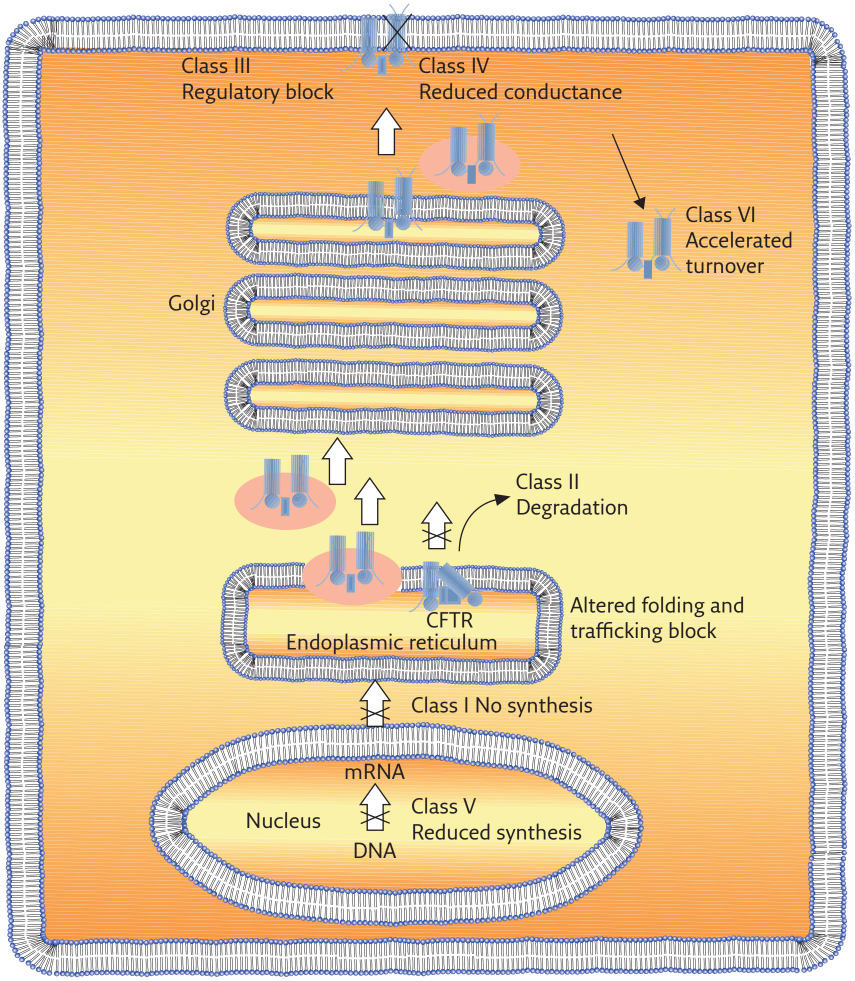

Class III
Regulatory block
Class IV
Reduced conductance
Class VI
Accelerated
turnover
Golgi
Class II
Degradation
CFTR
Endoplasmic reticulum
Altered folding and
trafficking block
Class I No synthesis
mRNA
Nucleus
Class V
Reduced synthesis
DNA

Figure 1. Classes of CFTR gene mutations. Class I: no functional CFTR protein synthesis (nonsense, frameshift; e.g. p.Gly542X); class II: protein folding and trafficking defect (missense, amino-acid deletion; e.g. p.Phe508del); class III: defective channel regulation (missense, amino-acid change; e.g. p.Gly551Asp); class IV: decreased channel conductance (missense; amino-acid change; e.g. p.Arg117His); class V: reduced protein synthesis (splicing defect, missense; e.g. 3849+10kbC→T); class VI: decreased CFTR stability with faster turnover (missense, amino-acid change; e.g. p.Gln1412X). Acknowledgement: Andrew Bush and Jane C. Davies.

The accuracy of sweat chloride measurements is operator dependent, so it is critical that testing is performed in experienced centres, following standard guidelines. If further CF functional testing is needed (nasal potential difference (NPD) and intestinal current measurement (ICM)), it should be performed in a validated and certified reference centres with trained staff.

Sweat chloride <30 $\mathrm{mmol \cdot L^{-1}}$ is considered normal. This result is sufficient to rule out CF in most individuals (CF diagnosis ‘unlikely’). Nonetheless, in patients with symptoms strongly suggesting CF, repeating sweat chloride and/or DNA testing may be warranted. This is because a normal sweat chloride concentration is observed in

Table 1. Common clinical scenarios in late presentation of CF

Recurrent chest infections	Consider if responsible pathogens are "suggestive" microorganisms, *e.g. Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Burkholderia cepacia* complex
Widespread bronchiectasis	Especially if involving upper lobes, with extrapulmonary features, positive family history, or infection with 'suggestive' microorganisms (see above)
Poorly controlled or 'atypical' asthma	Especially if chronic productive cough, and a poor response to standard asthma therapy
Recurrent isolates of nontuberculous mycobacterial or fungal species in sputum cultures	Particularly *Mycobacterium abscessus* spp. and non-*Aspergillus* fungal species (*e.g. Exophiala dermatitidis*, *Scedosporium apiospermum*, *Scedosporium prolificans*)
Nasal polyps, severe chronic rhinosinusitis	Exclude other causes
Male infertility	Azoospermia due to congenital bilateral absence of the vas deferens (CBAVD)
Acute pancreatitis (recurrent)	Usually seen in pancreatic-sufficient CF patients
Pancreatic exocrine insufficiency	Rare in late presentation
Electrolyte disturbances	Acute dehydration due to heat prostration, hypochloraemic metabolic alkalosis, pseudo-Bartter syndrome
Hepatobiliary disease	Hepatic steatosis, cirrhosis and non-cirrhotic portal hypertension, chronic liver failure
Cascade screening	Diagnosis made in a relative leading to extended family screening

Table 2. Diagnostic criteria for CF: both clinical suspicion plus evidence of CFTR dysfunction must be present

Clinical suspicion	**Evidence of CFTR dysfunction**
≥1 clinical manifestation	Positive sweat chloride test (i.e. ≥60 $\text{mmol}\cdot\text{L}^{-1}$)
or	or
Positive newborn screening	Two disease-causing mutations in CFTR (one from each parental allele)
or	or
Positive family history	Abnormal NPD or ICM (from *ex vivo* rectal biopsy) testing

~1% of patients with CF, who have unusual genotypes such as the 3849+10kbC→T or poly-T defects. Sweat chloride 30–59 mmol·L^{-1} is intermediate and requires further evaluation, by performing CFTR sequencing and/or ancillary functional testing using NPD or ICM to confirm/exclude the diagnosis of CF.

DNA testing is not mandatory to make the diagnosis in the presence of a positive sweat chloride test. However, gene sequencing is recommended for all patients, as the knowledge of the specific CFTR genotype has important implications for treatment and prognosis.

Finally, in the context of the diagnostic assessment, ancillary tests, like faecal elastase for pancreatic insufficiency, HRCT for bronchiectasis and scrotal ultrasound or semen analysis for CBAVD, may be useful to objectify occult clinical manifestations of CF.

Management of CF

CF is a multisystem disease. Treatment can only be optimally delivered with the help of a full multidisciplinary team (CF adult pulmonologist, specialist nurse, physiotherapist, dietician, social worker, clinical psychologist and pharmacist) and the help of ancillary specialists with expertise in CF (thoracic surgeon, gastroenterologist, radiologist, ENT surgeon, obstetrician and endocrinologist). CF patients should be seen at least every 3 months by the core CF team, with regular assessment of clinical conditions, lung function, pulse oximetry, nutritional status and airways microbiology (table 3). A large number of treatment guidelines have been published.

Lung disease

The main issues are prevention of cross-infection by individual segregation and aggressive use of antibiotics. Oral antibiotics are used prophylactically in some countries to prevent *S. aureus* infection, despite the concerns of an increased risk of *P. aeruginosa* infection. Ensuring eradication of *P. aeruginosa* at the time of the first positive culture is an important priority in CF care. Different protocols are available, with both systemic or inhaled antibiotics, and reported eradication rates of 70–80%. Chronic suppressive antimicrobial therapy with inhaled tobramycin, colistin, aztreonam lysine and levofloxacin is recommended for those who become chronically colonised by *P. aeruginosa*.

Based on good theoretical principles, chest physiotherapy to increase sputum production represents one of the mainstays of treatment. However, there are only a few appropriately powered randomised controlled trials to support the use of airway clearance.

People with CF suffer from recurrent episodes of pulmonary exacerbations. Pulmonary exacerbations are critical events in CF natural history, requiring aggressive interventions and affecting patients' quality of life. Frequent exacerbations are associated with reduced survival and increased decline in lung function. Moreover, ~25% of patients do not return to their pre-exacerbation lung function. Inhaled antibiotics, chronic azithromycin and mucolytic therapies (*i.e.* DNase, hypertonic saline and mannitol) have been shown to reduce the frequency of exacerbations.

Gastrointestinal disease

The main issues are to ensure optimal nutrition and be alert to gastrointestinal causes of weight loss that are unrelated to pancreatic insufficiency. Bad nutritional state is a very poor prognostic feature. CF patients have higher than normal energy requirements because of subclinical malabsorption and a higher energy consumption

Table 3. Management of CF lung disease

Disease stage	Pulmonary status	Aim	Management
Early (unusual, but seen in adults with milder forms of CF)	Pre-infection	Mucus clearance	Airway clearance techniques (physiotherapy and adjuncts) Physical exercise Mucolytics (*e.g.* inhaled rhDNase, 7% hypertonic saline and mannitol)
		Prevent infection	Segregation and cohorting to prevent cross-infections Prophylactic antibiotics are controversial Influenza vaccination
	Airways obstruction	Symptomatic relief	No evidence supporting the use of LABA, apart from in combination with ICS for patients with demonstrated airway hyperreactivity SABA usually prescribed on an as needed basis and before use of inhaled mucolytics/antibiotics and physiotherapy
	Intermittent isolation of *P. aeruginosa*	Eradication of infection	High doses of appropriate antibiotics *P. aeruginosa* eradication protocols include both topical (nebulised) and systemic (usually oral ciprofloxacin)
Intermediate	Chronic infection with usual organisms (*P. aeruginosa, S. aureus* (methicillin sensitive and resistant)	Suppression of bacterial load and, thus, limitation of the inflammatory response	Depends on organism: for *P. aeruginosa* inhaled antimicrobial agents are available including tobramycin, colistin, aztreonam lysine and levofloxacin New, faster nebuliser devices and dry powder formulations available for different agents Oral flucloxacillin controversial for *S. aureus*

(*Continued*)

Table 3. Continued

Disease stage	Pulmonary status	Aim	Management
		Treat infective exacerbations	Oral or intravenous antibiotics Standard duration of treatment: 14 days (although no strong evidence to support this length of treatment) Some centres use regular elective courses, but no evidence to prefer this over symptomatic use Culture results usually guide choice; no evidence for benefit from antimicrobial sensitivity testing, particularly for *P. aeruginosa*
	Hyper-inflammatory state	Reduce airways inflammation	Long-term oral azithromycin useful for frequent exacerbators (test for NTM in sputum before starting) Evidence lacking for high-dose ibuprofen in adults No evidence for routine use of corticosteroids (inhaled and systemic)
	ABPA	Treat and prevent recurrence	Oral corticosteroids (long course often required), consider pulsed methylprednisolone Addition of an antifungal agent (azoles) is common, but evidence limited Poor evidence for omalizumab efficacy
	Infection with less common organisms (*Burkholderia cepacia* complex, *S. maltophilia*, *A. xylosoxidans*) and multidrug-resistant strains	Prevention by segregation Treat exacerbations and monitor long-term related outcomes	Confirm diagnosis in a reference laboratory Treat on an individual basis with specialist microbiological advice Evidence-based protocols for eradication attempts and/or chronic suppressive therapies not available
	NTM infections	Treat when evidence of NTM-pulmonary disease (consider implications from *M. abscessus* spp. for lung transplantation)	Diagnosis and management difficult; seek specialist advice, especially for *M. abscessus* spp. infection Prolonged courses of multiple antimicrobials will be needed: ethambutol, rifampicin, macrolides, quinolones, tetracyclines and amikacin are among the agents used

(*Continued*)

Table 3. Continued

Disease stage	Pulmonary status	Aim	Management
	Fungal disease (*Aspergillus* bronchitis, non-*Aspergillus* infections)	Treat exacerbations and monitor long-term related outcomes	Diagnosis and management difficult Poor evidence available Seek specialist advice; consider antimicrobial sensitivity testing to guide treatment choices and routine performance of therapeutic drug monitoring Duration of treatment (usually azoles) not established
	Lobar or segmental atelectasis (may be seen at any stage of CF)	Re-inflation of the lung	Intensive physiotherapy, with combined rhDNase, hypertonic saline and mannitol as appropriate Intravenous antibiotics Fibre-optic bronchoscopy; consider endobronchial instillation of rhDNase if conventional management fails
Advanced	Major haemoptysis (may also be seen in those with well-preserved lung function)	Prevent or halt acute bleeding	Admit for intravenous antibiotics and tranexamic acid Bronchoscopy usually not useful Bronchial artery embolisation for ongoing bleeding Lobectomy is a last resort
	Pneumothorax	Control air leak, prevent recurrence	Conservative management for trivial pneumothoraces, otherwise tube drainage Early surgery and pleurodesis if does not respond rapidly
	End-stage respiratory failure	Advanced lung disease management	Optimise conventional treatment Consider long-term intravenous antibiotics or elective frequent admissions Long-term oxygen therapy Consider high-flow oxygen and NIV Referral for lung transplantation as early as possible Extracorporeal membrane oxygenation can be used as a bridge to transplantation
		End-of-life care	Collaboration with palliative care team is strongly encouraged

RhDNase: recombinant human DNase; LABA: long-acting β_2-adrenergic receptor agonists; ICS: inhaled corticosteroids; SABA: short-acting β_2-adrenergic receptor agonists; NTM: nontuberculous mycobacteria; ABPA: allergic bronchopulmonary aspergillosis.

secondary to infection. Increased metabolic rate is thought by some to be part of the underlying defect. Weight should be measured, and body BMI calculated, at every clinic. For CF adults, target BMI is ≥ 22 kg·m^{-2} for females and ≥ 23 kg·m^{-2} for males.

Improved survival of CF patients will lead to an increased number of patients affected by advanced liver disease. Moreover, CF is associated with an increased risk of digestive tract malignancies. Regular screening with colonoscopy every 5 years is recommended for patients >40 years (table 4).

Other organ system disease

It is important to be aware that new complications are being described as CF patients survive longer (table 5). A full systems review is essential at each clinic visit. Finally, the psychological aspects of CF related to the effects of chronic illness and the burden of disease and its treatment should not be underestimated.

Treatment with CFTR modulators

Over the past decade, a new class of small molecules called 'CFTR modulators' has been developed and licensed for clinical use. These drugs act by improving intracellular processing (correctors) and function (potentiators) of the defective CFTR protein and are an important advance in management of CF because they target the production or function of mutant CFTR protein rather than its downstream consequences. The indications and efficacy of these drugs depend upon the CFTR gene variant in the individual patient.

Ivacaftor, the first CFTR potentiator, was specifically designed to treat patients with at least one p.Gly551Asp mutation in their CFTR genes. Its use has been licensed by the US Food and Drug Administration for a total of 38 relatively rare gating and residual function mutations. Ivacaftor was associated with significant improvement in FEV_1 and nutritional status, and a reduction in pulmonary exacerbations and sweat chloride values.

Lumacaftor and tezacaftor, two correctors of intracellular CFTR trafficking, have been both tested and licensed for use in combination with ivacaftor for patients homozygous for p.Phe508del mutations and for those with at least one residual function mutation (only tezacaftor/ivacaftor). Only modest effects on lung function and pulmonary exacerbations were noticed among patients with p.Phe508del homozygous mutations.

Recently, two phase 3 clinical trials with a triple combination of two correctors and a potentiator (elexacaftor/tezacaftor/ivacaftor) showed remarkable effects among patients with two copies of p.Phe508del or compound heterozygotes for p.Phe508del and one other minimal function mutation.

Several other drugs aimed at restoring CFTR function are in the pipeline. However, in the development of these drugs there have been a number of findings in clinical trials that suggest that targeted therapies are not entirely straightforward, some of the drugs may not be effective in all patients with a particular mutation and the benefit for some mutations may be age-related. These treatments also come at a high cost to the healthcare system and some have significant adverse effects and drug–drug interactions that preclude treatment or require discontinuation. Finally, it is important is to ensure that the basic therapy, which has so greatly improved prognosis, is not neglected.

Table 4. Management of CF gastrointestinal manifestations in the adult

Organ	Manifestation	Management
Pancreas	Exocrine insufficiency (malabsorption, steatorrhoea)	High fat hypercaloric diet Supplementation with enteric coated microsphere pancreatic enzymes and fat-soluble vitamins (A, D, E, K) Fat absorption may be aided by alkaline environment (H_2-receptor blockers or PPI) Nutritional supplements as appropriate Gastrostomy feeds if nutritional failure (parenteral nutrition only rarely required)
	Acute (recurrent) pancreatitis (usually, but not only, among pancreatic-sufficient patients)	As for other causes
Oesophagus/ stomach	Gastro-oesophageal reflux disease (particularly post-lung transplant); gastroparesis	PPI, prokinetic agents Consider surgery for refractory cases
Small bowel	DIOS	Intestinal lavage orally or by NGT with balanced electrolyte solution Hyperosmolar laxatives (*e.g.* gastrograffin) orally or by NGT Consider also hyperosmolar enema Severe acute cases, relieve with colonoscopy Laparotomy only as a last resort Review dose of and adherence to PERT
	Coeliac disease	Reported higher incidence in CF
	IBD (particularly Crohn's disease)	Treat as for standard care Seek gastroenterologist advice for better management
Colon	Constipation	Differential diagnosis with DIOS Laxatives; high-fibre diet Recommend proper daily water intake
	Fibrosing colonopathy	Review dose of PERT
	Colorectal cancer	Higher incidence in CF Screening colonoscopy every 5 years in patients ≥40 years old
Liver, biliary tract	CFLD (wide spectrum including hepatic steatosis, non-cirrhotic portal hypertension, focal biliary cirrhosis, liver failure)	Annual screening for CFLD (LFTs, ultrasound) UDCA controversial Referral for liver transplantation for patients with end-stage disease
	Gallbladder disease, sclerosing cholangitis	UDCA, consider prophylactic cholecystectomy

PPI: proton pump inhibitors; DIOS: distal intestinal obstruction syndrome; NGT: nasogastric tube; PERT: pancreatic enzyme replacement therapy; IBD: inflammatory bowel diseases; CFLD: CF-related liver disease; LFTs: liver function tests; UDCA: ursodeoxycholic acid.

Table 5. Treatment of other common clinical manifestations of CF in adults

Organ	Manifestation	Management
Upper airways	Chronic rhinosinusitis (with exacerbations), nasal polyps (possibly leading to OSA)	Topical steroids and antibiotics (poor evidence concerning duration and protocols) Regular drainage ENT surgery if medical management fails (re-operation often needed)
Endocrine pancreas	CFRD	Annual screening with OGTT recommended Increasingly, continuous glucose monitoring used for screening Start insulin at diagnosis; continue high-fat diet, adjusting insulin accordingly Potential benefits from early start with insulin even in patients with dysglycaemia (*e.g.* INDET or IGT at OGTT) and poor control of nutritional status and lung function No evidence for oral hypoglycaemic agents Regular monitoring of microvascular complications (macrovascular ones are relatively rare)
Bones and joints	Osteoporosis	Regular monitoring of vitamin D levels (at least once per year) and bone density (at least once every 2 years) Proper calcium and vitamin D supplementation Treatment with bisphosphonates, monoclonal antibodies (*e.g.* denosumab) and recombinant PTH as for other causes
	CF arthropathy	NSAIDs and/or corticosteroids when appropriate Seek specialist rheumatological advice for severe disease
Male reproductive tract	Bilateral absence of vas deferens leading to male infertility	Sperm aspiration and *in vitro* fertilisation Genetic counselling prior to procedure advisable
Female reproductive tract	Stress incontinence	Pelvic floor exercises Seek gynaecological advice
	Pregnancy (not an illness, but may be a major therapeutic challenge); women with severe CF may be subfertile, but normal conception is usual	Pre-pregnancy genetic counselling advisable Continue standard CF medications Close collaboration with obstetric unit is essential May need regular admissions to hospital for intravenous antibiotics Especially beware if low lung function prior to pregnancy and CFRD

CFRD: CF-related diabetes; OGTT: oral glucose tolerance test; INDET: indeterminate glycaemia, *i.e.* 1-h plasma glucose peak >200 mg·dL^{-1} (11.1 mmol·L^{-1}); IGT: impaired glucose tolerance, *i.e.* 2-h plasma glucose 140–200 mg·dL^{-1} (7.8–11.1 mmol·L^{-1}); PTH: parathyroid hormone; NSAIDs: nonsteroidal anti-inflammatory drugs.

Transplantation

Despite a remarkable improvement in median survival, CF remains a lethal disease and lung transplantation still represents the only effective treatment available for those with end-stage pulmonary disease. However, mortality on waiting lists is still high.

The latest guidelines from the US CF Foundation recommend early referral for transplant assessment. FEV_1 <30% of predicted alone is considered a sufficient criterion to undergo transplant referral. However, patients with FEV_1 <40% predicted should be referred when markers of shortened survival (*i.e.* reduced exercise tolerance, hypoxaemia, hypercarbia, pulmonary hypertension), poor nutritional status (BMI <18 $kg \cdot m^{-2}$), frequent or severe pulmonary exacerbations, massive haemoptysis (>240 mL) or pneumothorax are found. Special consideration should be given to female patients, due to the well-known gender gap in CF, and in those individuals with short stature due to technical difficulties in finding proper donors. Also, accelerated decline in lung function (>20% relative decline in FEV_1 within 12 months) represents an indication for transplant referral, even among patients with relatively preserved basal lung function (FEV_1 up to 50% of predicted).

Malignancy within 2 years, major organ dysfunction (*e.g.* kidney or heart), severe skeletal deformities, poor treatment adherence, untreatable psychological conditions, lack of consistent social support and substance addiction are considered contraindications to lung transplant. Most transplant centres do not accept patients infected with *Burkholderia cepacia* complex, particularly *Burkholderia cenocepacia*, or *M. abscessus* spp.

End-of-life treatment strategies should be considered in the advanced stage of disease when lung transplantation is not available or contraindicated.

Further reading

- Bell SC, *et al.* (2015). New pharmacological approaches for cystic fibrosis: promises, progress, pitfalls. *Pharmacol Ther*; 145: 19–34.
- Burgel PR, *et al.* (2015). Future trends in cystic fibrosis demography in 34 European countries. *Eur Respir J*; 46: 133–141.
- Castellani C, *et al.* (2018). ECFS best practice guidelines: the 2018 revision. *J Cyst Fibros*; 17: 153–178.
- Dellon EP, *et al.* (2016). Advance care planning in cystic fibrosis: current practices, challenges, and opportunities. *J Cyst Fibros*; 15: 96–101.
- Elborn JS (2016). Cystic fibrosis. *Lancet*; 388: 2519–2531.
- Elborn JS (2018). CFTR modulators: deciding what is best for individuals in an era of precision medicine. *Ann Am Thorac Soc*; 15: 298–300.
- Elborn JS, *et al.* (2016). Report of the European Respiratory Society/European Cystic Fibrosis Society task force on the care of adults with cystic fibrosis. *Eur Respir J*; 47: 420–428.
- Elborn JS, *et al.* (2017). Clinical trial research in focus: ensuring new cystic fibrosis drugs fulfil their potential. *Lancet Respir Med*; 5: 681–683.
- Farrell PM, *et al.* (2017). Diagnosis of cystic fibrosis: consensus guidelines from the cystic fibrosis foundation. *J Pediatr*; 181S: S4–S15.

- Langton Hewer SC, *et al.* (2017). Antibiotic strategies for eradicating *Pseudomonas aeruginosa* in people with cystic fibrosis. *Cochrane Database Syst Rev*; 4: CD004197.
- Liou TG (2019). The clinical biology of cystic fibrosis transmembrane regulator protein: its role and function in extrapulmonary disease. *Chest*; 155: 605–616.
- Mogayzel PJ Jr, *et al.* (2013). Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*; 187: 680–689.
- Nick JA, *et al.* (2005). Manifestations of cystic fibrosis diagnosed in adulthood. *Curr Opin Pulm Med*; 11: 513–518.
- Ramos KJ, *et al.* (2019). Lung transplant referral for individuals with cystic fibrosis: Cystic Fibrosis Foundation consensus guidelines. *J Cyst Fibros*; 18: 321–333.

Main patient registries reports

- Cystic Fibrosis Foundation Patient Registry. 2017 Annual Data Report. www.cff.org/Research/Researcher-Resources/Patient-Registry/2017-Patient-Registry-Annual-Data-Report.pdf
- Canadian Cystic Fibrosis Registry. 2017 Annual Data Report. www.cysticfibrosis.ca/uploads/Registry%20Report%202017/2017%20Registry%20Annual%20Data%20Report.pdf
- UK Cystic Fibrosis Registry. 2017 Annual Data Report. www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/reporting-and-resources
- ECFS Patient Registry. 2016 Annual Data Report. www.ecfs.eu/sites/default/files/general-content-images/working-groups/ecfs-patient-registry/ECFSPR_Report2016_06062018.pdf

Recommended weblinks

- The UK Cystic Fibrosis Gene Therapy Consortium www.cfgenetherapy.org.uk
- Cystic Fibrosis Mutation Database www.genet.sickkids.on.ca
- Clinical and Functional Translation of CFTR (CFTR2) www.cftr2.org
- Cystic Fibrosis Foundation: Drug Development Pipeline www.cff.org/Trials/Pipeline
- Cystic Fibrosis Database www.cfdb.eu

Primary ciliary dyskinesia

Jane S. Lucas and Woolf T. Walker

Primary ciliary dyskinesia (PCD) is a genetically and clinically heterogeneous disorder, usually inherited as an autosomal recessive condition. Whilst the prevalence is difficult to ascertain because of underdiagnosis, it is estimated to affect one in 10000 in Europeans, and more in consanguineous populations. PCD is characterised by progressive lung disease that typically starts in infancy, rhinosinusitis and infertility; 50% have *situs* abnormalities.

Pathophysiology

Ciliated epithelial cells line the upper and lower airways, Eustachian tubes, Fallopian tubes, and ventricles in the brain (figure 1a). In healthy individuals, the coordinated beating of airway cilia moves debris and pathogen-laden mucus (mucociliary clearance) to the oropharynx where it is swallowed or expectorated (figure 1b).

In patients with PCD, defects in the ciliary ultrastructure or function lead to loss of the coordinated cilia beat pattern and hence impair mucociliary clearance. Biallelic mutations in >39 genes have been reported to cause PCD but these genes only account for ~70% of cases, so many more genes are yet to be discovered. Genes encoding proteins in the outer dynein arm are most commonly affected (figure 1a). These dynein motors drive ciliary beating through ATPase activity and defects can cause cilia to be static or have minimal movement. Mutations affecting the radial spoke head components, the central pair or the nexin dynein regulatory complex also cause dyskinetic cilia (figure 1a). Mutations in genes controlling generation of cilia severely reduce numbers of cilia. In all cases, there is failure of mucociliary clearance leading to chronic and recurrent infections with associated inflammation.

Key points

- Primary ciliary dyskinesia (PCD) is a genetically and clinically heterogeneous disorder of motile cilia, usually inherited as an autosomal recessive disorder.
- Respiratory and nasal symptoms typically start in infancy, followed by progressive suppurative lung disease, persistent rhinosinusitis, serous otitis media and infertility; organ laterality defects occur in ~50% of cases.
- Specialist reference centres conduct a combination of diagnostic tests.
- There is paucity of evidence for treating PCD, and expert statements emphasise the need for a multidisciplinary approach to regular airway clearance therapy, hearing support and treatment of infections.

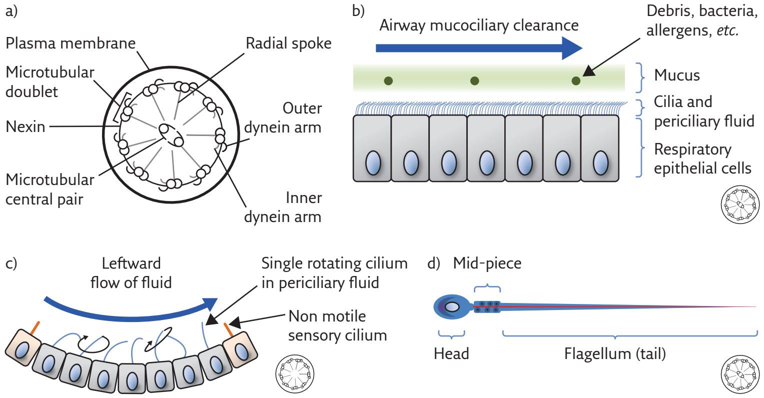

a)
Plasma membrane
Radial spoke
Microtubular doublet
Nexin
Outer dynein arm
Microtubular central pair
Inner dynein arm
b)
Airway mucociliary clearance
Debris, bacteria, allergens, *etc.*
Mucus
Cilia and periciliary fluid
Respiratory epithelial cells
c)
Leftward flow of fluid
Single rotating cilium in periciliary fluid
Non motile sensory cilium
d) Mid-piece
Head
Flagellum (tail)

Figure 1. a) Diagram of a motile cilium with '9+2' microtubular structure, shown in transverse section as seen by transmission electron microscopy. b) Coordinated beating of cilia clears mucus, bacteria and debris to the oropharynx to be swallowed; airway cilia have a '9+2' structure. c) The ventral node is a tiny pit lined with cells with single motile cilia that helps the developing embryo create left–right asymmetry. These cilia with '9+0' structure rotate clockwise, creating a leftward flow of fluid. Sensory cilia on the edge of the node respond to the flow, triggering a cascade of signalling proteins. d) The sperm flagellum mid-piece and tail have '9+2' microtubular structure important for motility.

Motile cilia on the embryonic node are essential for determining left–right body asymmetry; hence, ~50% of people with PCD have *situs inversus* or heterotaxia (figure 1c). The sperm flagellum has a similar ultrastructure to the cilium, causing male infertility (figure 1d), whilst immotile cilia in the Fallopian tubes are responsible for female subfertility in PCD.

Clinical symptoms and diagnosis

Since the combination of diagnostic tests is expensive and only available in specialist centres, identifying appropriate patients for testing is important (table 1). The disease is heterogeneous with only some patients having all symptoms. Neonates typically present with respiratory distress at term, starting a few hours after birth, and neonatal rhinitis is common. Daily wet cough typically starts in the first year and persists throughout life, complicated by infective exacerbations. In fact, patients without a daily wet cough are highly unlikely to have PCD. Lower- and middle-lobe bronchiectasis can start in infancy and is usual by adulthood. Most patients have persistent rhinosinusitis and serous otitis media is often associated with fluctuating impaired hearing particularly during childhood. Male and, to a lesser extent, female infertility is common. *Situs inversus* occurs in ~50% and heterotaxy in ~10% of patients, with congenital heart disease occurring in 5–6% of patients.

With no single 'gold standard' diagnostic test, confirming the diagnosis of PCD can be challenging. European Respiratory Society (ERS) and North American guidelines recommend a combination of tests conducted in centres with extensive experience of normal and abnormal findings. Nasal brushing samples of ciliated epithelia for microscopy should be obtained when the patient has been free of respiratory infections for ≥4 weeks to avoid the risk of poorly ciliated samples and secondary dyskinesia. Tests include measurement of nasal nitric oxide (nNO) (which is almost always $<77\ \text{nL}\cdot\text{min}^{-1}$ in PCD), high-speed video microscopy analysis (HSVMA) of ciliary

Table 1. ERS guidelines for who to refer for PCD diagnostic testing

Patients should be tested for PCD if they have several of the following features
Persistent wet cough *Situs* anomalies Congenital cardiac defects Persistent rhinitis Chronic middle ear disease with or without hearing loss A history in term infants of neonatal upper and/or lower respiratory symptoms
Patients with normal *situs* presenting with other symptoms suggestive of PCD should be referred for diagnostic testing
Siblings of patients should be tested for PCD, particularly if they have suggestive symptoms
The use of combinations of distinct PCD symptoms and predictive tools (*e.g.* PICADAR) is recommended

beat frequency and pattern (both on the original sample and following cell culture), transmission electron microscopy (TEM) of ciliary ultrastructure, immunofluorescent labelling of ciliary proteins, and genetic testing. Historically, TEM was considered the gold standard test for the diagnosis of PCD but we now appreciate that 10–15% of patients with PCD have normal ciliary ultrastructure, as resolvable by TEM. The diagnosis can therefore be confirmed when a hallmark TEM ultrastructural defect is seen or a known biallelic mutation in a PCD-causing gene is found but is considered highly likely in those with a compelling clinical history, very low nNO and consistently abnormal HSVMA.

Treatment and follow-up

As there is no cure for PCD, its management aims to optimise health, social and psychological wellbeing, whilst preventing progression of lung damage, with a multidisciplinary team approach. There is, however, a paucity of evidence for optimal management, with only one published randomised trial on its treatment to date. As a result, patient care is usually based on experience from other diseases (*e.g.* CF or chronic rhinosinusitis) despite differing underlying pathophysiology.

Following a diagnosis of PCD, immediate care includes initiating management of this lifelong condition, genetic and fertility counselling where appropriate, and organising further assessments to investigate abdominal and thoracic *situs*, comorbidities and complications (*e.g.* echocardiographic, otorhinolaryngological and audiological assessment). Baseline investigations such as spirometry, audiometry, sputum culture and chest imaging should be followed by regular appointments to monitor and manage disease progression.

Airway clearance physiotherapy is key to lower airway management, aiming to clear mucus, and minimise infections, atelectasis and progressive respiratory impairment. It should be undertaken at least once to twice daily, increasing at times of respiratory exacerbations. Techniques include breathing manoeuvres, manual techniques, positive expiratory pressure (PEP) adjuncts and oscillatory PEP. Nebulised hypertonic saline is often prescribed as a mucolytic adjunct to physiotherapy, anecdotally providing good benefit to some patients. In addition, physical exercise should be strongly encouraged.

Management and prevention of pulmonary infections requires regular microbiological surveillance and treatment of lower airway exacerbations. *Haemophilus influenzae* is the most common pathogen, whilst *Pseudomonas aeruginosa, Streptococcus pneumoniae, Moraxella catarrhalis* and *Staphylococcus aureus* are also prevalent. Prophylactic antibiotic therapy with azithromycin is beneficial in CF and non-CF bronchiectasis, and its efficacy is currently under investigation in PCD. Until there is more evidence for treatment of lower airway pathogens in PCD, most physicians follow CF guidelines with modifications to doses of antibiotics, which are generally higher in CF. Experts recommend prevention of infection by immunisation including *S. pneumoniae* and annual influenza vaccination.

In advanced lung disease, the physician should consider oxygen therapy, NIV and lung transplantation where appropriate.

Active and passive smoking must be discouraged.

Management of the upper airways lacks evidence. Therefore, guidelines from chronic rhinosinusitis in the general population are usually followed. Management includes sinonasal irrigation with saline, treatment of infections, trials of response to nasal steroids and, in refractory cases, consideration of sinus surgery.

Hearing impairment often requires hearing aids. Insertion of ventilation tubes is controversial because troublesome otorrhoea complicates 30% of surgery in comparison to 5% in the general population.

Infertility is common and PCD patients require access to a specialised fertility clinic.

Anaesthetic complications from atelectasis during surgical procedures should be avoided by careful preoperative assessment, perioperative physiotherapy and antibiotics.

Further reading

- Kuehni CE, *et al.* (2017). Diagnosis of primary ciliary dyskinesia: summary of the ERS Task Force report. *Breathe*; 13: 166–178.
- Lucas JS, *et al.* (2017). Clinical care of children with primary ciliary dyskinesia. *Expert Rev Respir Med*; 11: 779–790.
- Shapiro AJ, *et al.* (2016). Diagnosis, monitoring, and treatment of primary ciliary dyskinesia: PCD Foundation consensus recommendations based on state of the art review. *Pediatr Pulmonol*; 51: 115–132.

α_1-antitrypsin deficiency

Robert A. Stockley

α_1-antitrypsin deficiency (AATD) is the most recognised genetic condition associated with the development of emphysema in both smokers and never-smokers. Over 500 genetic variants have been described, many of which seem to produce a fully functional protein. Several variants have been associated with reduced plasma concentrations. By far the most common critically low deficiency state is referred to as PiZZ (proteinase inhibitor homozygous for the Z protein genotype reflecting a point mutation resulting in a single amino acid change, Glu342 to Lys). Other deficiency variants are caused by genetic frameshifts or nucleotide substitutions that lead to premature stop codons causing incomplete protein production and secretion failures. These result in no protein secretion into the blood (the so-called null variants). The prevalence of the PiZZ deficiency variant across Europe varies from one case in 1600 persons in the Baltic States to one case in 3000–5000 persons following Viking migration pathways (Stockley *et al.*, 2013).

The protein is made predominantly in the liver, but the Z protein is retained because of its propensity to polymerise spontaneously resulting in retention in the endoplasmic reticulum and hence low circulating and lung concentrations.

Pathophysiology

α_1-antitrypsin (AAT) is the main circulating inhibitor of serine proteinases. The neutrophil contains several such enzymes that are released as the cell becomes activated and enter the lung where they facilitate cell migration through the connective tissues by proteolytic degradation. The low concentration of AAT in deficiency states fails to control these enzymes adequately at the point of release. This is most critical in the intricate alveolar structures of the lung where it leads to excess degradation of lung elastin leading to emphysema.

Key points

- Although the classical α_1-antitrypsin deficiency patient is one with early onset basal panlobular emphysema, the clinical phenotype may be typical of non-deficient COPD.
- All patients with a diagnosis of COPD or adult-onset asthma should be tested.
- A simple blood test provides evidence of low level of α_1-antitrypsin (AAT) indicative of deficiency. Note the AAT level in carriers is often in the normal range.
- All patients should be referred and seen at least once in a specialist clinic.

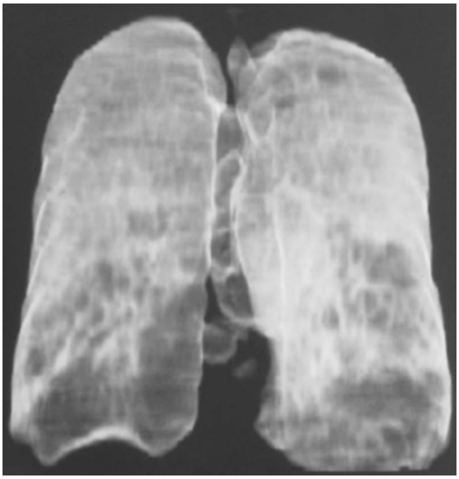


Figure 1. Three-dimensional CT image of the classical distribution of low density (emphysema) at the lung bases.

Clinical features

The predominant association is with early onset of emphysema particularly (although not exclusively) in the lower zones, especially in smokers. This leads to an early reduction in gas transfer and subsequent reduction in airflow as defined by the FEV1 and FEV1/FVC ratio (Holme *et al.*, 2013). Further progression also leads to air trapping resulting in an increase in residual volume and TLC. CT demonstrates panlobular emphysema in the lower zones (figure 1), although in up to 30% of cases the distribution may be in the upper zones and centrilobular in nature as seen in non-AATD COPD.

The retention and build-up of polymerised AAT in the hepatocyte causes cellular stress and damage, and may present as neonatal jaundice and occasionally fulminant hepatic failure as well as clinical cirrhosis in adults. Other associations include panniculitis, systemic vasculitis and ulcerative colitis (Stone *et al.*, 2014).

Diagnosis

Circulating AAT is critically reduced to <20% of the normal level in subjects with the Z homozygosity and Znull heterozygotes. No AAT is detected in null/null homozygotes. Protein isoelectric focusing characteristics can identify the Z protein (phenotyping) and other variants where the protein is secreted. The normal variant is labelled M and the other most common variant is S, leading to MS heterozygotes (most common in the Mediterranean countries) that are associated with a concentration of AAT about 80% of the normal level and SZ heterozygotes in whom the AAT concentration is about 30% of the normal level. The level at which there is an increased risk of developing COPD seems to be about 20% of the normal level of AAT, suggesting that most SZ patients are not really at increased risk and are most likely to have a normal COPD and the emphysema clinical phenotype. The null variants cannot be seen on isoelectric phenotyping leading to the false assumption that M, S and Z null heterozygotes are M, S and Z homozygotes. This leads to some confusion over the importance and inheritance of the variants. However, a lower plasma level than expected should raise suspicions. Gene sequencing identifies the specific abnormality and is therefore becoming the investigation of choice among specialists. The inheritance is co-dominant for the Z variant enabling screening strategies and patient education (figure 2).

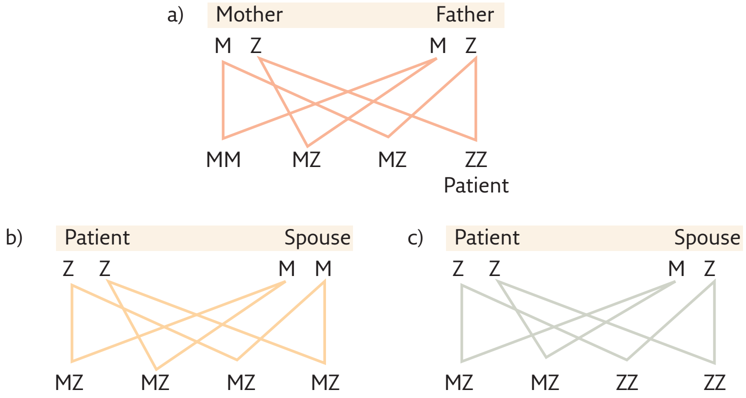


Figure 2. Co-dominant inheritance of AAT genes. a) The probable family history of a patient identified as PiZ, giving a one in four incidence of the siblings being PiM, a one in four incidence of PiZ and a two in four incidence of PiMZ. b) Implications for the patient with a 90–95% chance that their spouse will be normal (PiM), indicating that all children should be PiMZ. c) Implications if the patient marries a heterozygote (~3–5% chance). Again one allele will be passed to the child from each parent, with a one in two chance that offspring will be PiMZ and a one in two chance that offspring will be PiZ.

It is advised that all patients with COPD should be tested for AATD as well as individuals with an adult-onset diagnosis of asthma. This is because the condition can present with a non-deficient COPD clinical phenotype and the classical patient with early onset symptoms is often misdiagnosed as having asthma, especially if they do not smoke.

Treatment

The lung damage is treated along conventional lines for COPD. Never-smokers or ex-smokers who continue to progress can be treated with specific augmentation. This involves weekly intravenous infusions of AAT (available in many countries) restoring close to normal or 'protective' levels of the protein. This slows the progression of the lung destruction causing emphysema (Chapman *et al.*, 2015). Inexorable deterioration may require lung transplantation, or possible lung volume reduction either surgically or through the use of valves in suitable patients. Lung transplantation may not improve overall survival, but undoubtedly improves symptoms and lung function (Stone *et al.*, 2016). Liver transplantation for end-stage cirrhosis usually cures the deficiency.

All patients should be followed up either solely or jointly by specialists experienced in AATD where appropriate multidisciplinary clinics and transplantation services are available.

Further reading

- Chapman KR, *et al.* (2015). Intravenous augmentation treatment and lung density in severe α_1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015; 386: 360–368.
- Holme J, *et al.* (2013). Age related development of respiratory abnormalities in non-index alpha-1 anititrypsin deficient studies. *Respir Med*; 107: 387–393.

- Kalsheker N, *et al.*, eds. (2017). Alpha 1 Antitrypsin Deficiency: Biology, Diagnosis, Clinical Significance and Emerging therapies. London, Academic Press.
- Miravitlles M, *et al.* (2017). European Respiratory Society statement: diagnosis and treatment of pulmonary disease in α_1-antitrypsin deficiency. *Eur Respir J*; 50: 1700610.
- Stockley RA (2014). Alpha1-antitrypsin review. *Clin Chest Med*; 35: 39–50.
- Stockley RA, *et al.* (2013). Alpha-1 antitrypsin deficiency: the European experience. COPD; 10: Suppl. 1, 50–53.
- Stone H, *et al.* (2014). Disease associations in alpha-1-antitrypsin deficiency. *Respir Med* 2014; 108: 338–343.
- Stone HM, *et al.* (2016). Lung transplantation in alpha-1-antitryspin deficiency. *COPD*; 13: 146–152.
- WHO (1997). Alpha 1-antitrypsin deficiency: memorandum from a WHO meeting. *Bull World Health Organ*; 75: 397–415.

Occupational diseases

Johanna Feary and Paul Cullinan

Respiratory diseases arising directly from occupational exposures are a global and growing problem. Worldwide, an estimated 120000 men and women (~10% of all cases) die each year from occupational lung cancer, and new cases of occupational COPD and asthma account for the loss of 9 million and 2 million disability-adjusted life-years respectively. Each of these diseases, and indeed almost all occupational respiratory diseases, are readily preventable.

Because few clinicians have adequate training in the field and because most see few cases, specialist advice may be helpful.

Work-related asthma

Epidemiological surveys suggest that ~15% of adult asthma can be attributed to an exposure encountered at work. Clinicians should have a high index of suspicion for any patient presenting with adult-onset (or relapsed childhood) asthma, especially when this has occurred shortly after starting new employment.

Work-related asthma falls into three categories:

- 'Work-exacerbated asthma' (WEA) occurs in an individual with pre-existing asthma whose symptoms are provoked at work
- This must be carefully distinguished from 'occupational asthma' (OA), induced as a result of workplace exposure to a sensitising agent(s)
- Much less common is 'irritant-induced asthma' (IIA or reactive airway dysfunction syndrome) caused by a high-intensity exposure to a respiratory irritant at work.

Key points

- Clinicians should consider, in all adult patients, whether exposure in the workplace has been responsible for causing or exacerbating their respiratory disease.
- Clinicians should be familiar with the common causes of occupational asthma
- Silicosis, asbestosis and coal workers' pneumoconiosis are the commonest forms of pneumoconiosis, and can give rise to severe disability and death
- Occupational lung diseases are very largely preventable and their continued occurrence reflects a failure of societal resolve

Work-exacerbated asthma

WEA is not uncommon, particularly in those with suboptimal asthma control. Most frequently, the causes are respiratory irritants such as volatile chemicals and 'nuisance' dusts. Other triggers include physical exertion, cold temperatures (*e.g.* in the food industry) and changing shift patterns. In general, WEA is readily manageable by careful control of exposures at work and by optimising pharmacological treatment of their asthma; redeployment is rarely necessary.

Occupational asthma

OA may arise in workers with or without pre-existing asthma. ~400 workplace agents have been identified as respiratory sensitisers capable of inducing OA; most are airborne proteins or reactive chemicals (table 1).

Table 1. Common causes of OA

Exposure	Occupation
High molecular mass	
Animal proteins	
Live animals	Farming, poultry work, veterinary medicine, laboratory work
Food industry	Fish and seafood processing, egg processing
Enzymes	Detergent manufacture, cleaning, baking, food processing
Plant proteins	
Flour and cereal proteins	Baking, food processing
Tea, coffee, soybean, natural rubber latex, *etc.*	Baking, food and plants processing, healthcare, textile work
Low molecular mass	
Diisocyanates: toluene diisocyanate, hexamethylene diisocyanate, methylene diphenyldiisocyanate, *etc.*	Spray painting, foam manufacture, polyurethane work
Acid anhydrides: phthalic anhydride, maleic anhydride, *etc.*	Paint and plastic manufacture
Glues and resins: methacrylates, cyanoacyralates, epoxy resins, *etc.*	Plastic manufacture, material engineering, dental technology, nail parlour work, construction, *etc.*
Drugs: penicillins, opiates, *etc.*	Pharmaceutical manufacture
Abietic acid (colophony fume)	Electronic soldering
Wood dust: western red cedar, sapele, obeche, *etc.*	Woodwork
Dyes and bleaches, persulfates, reactive dyes	Hairdressing, textile work
Precious metals, platinum salts, *etc.*	Precious metal refining

Pertinent clinical features of OA include an initial period of 'latency' when the individual, while exposed to the sensitiser, is asymptomatic; and a subsequent, work-related pattern of symptoms that worsen at or after work and improve away from work, especially on holidays. In OA due to a workplace protein, rhinitis is universal and often precedes respiratory symptoms. The clarity of a work-related pattern of symptoms may be obscured by variable shift patterns, day-to-day differences in workplace exposures, isolated 'late' responses with symptoms occurring after work, symptoms from nonspecific triggers due to bronchial hyperresponsiveness that occurs with established OA, and pre-existing asthma.

For most protein allergens, it is possible to detect specific sensitisation using highly sensitive tests (serum specific IgE or skin-prick tests) available commercially or developed in a specialist laboratory. Such tests are also available for a limited number of chemical agents (*e.g.* acid anhydrides).

The most widely available investigative tool is serial measurement of peak flow. Measurements should be made at home and at work, at least four times a day over ≥4 weeks. With experienced readers, the technique has high sensitivity, specificity and positive predictive value. In difficult cases, specific inhalation challenge can be useful but few centres offer this as it requires specialist equipment and expertise.

Management of OA requires, in most cases, removal of or from exposure, as patients remain hypersensitive to minute levels of exposure and standard asthma therapy is of limited benefit. Accurate diagnosis, and distinction from WEA, is essential to avoid unnecessary consequences on careers. If identified early, OA is curable and the prognosis is good.

Irritant-induced occupational asthma

The mechanism underlying IIA is not immunological but reflects inflammation and repair; thus, individuals may encounter the initiating agent again without provoking symptoms. The diagnosis can be difficult, particularly if there is pre-existing asthma, and a measurement of nonspecific bronchial hyperresponsiveness is usually required. Standard asthma treatment is often ineffective.

Pneumoconiosis

The pneumoconioses are parenchymal diseases arising from inhalation of inorganic dusts at work. Some dusts are biologically inert and while they give rise to radiological shadowing, they are not associated with either clinical or functional disease. Others (notably asbestos, crystalline silica and coal mine dust) are fibrogenic, and give rise to characteristic radiological patterns and deficits in lung function. The pneumoconioses are generally diseases of long latency; importantly, they may progress long after exposure to the causative mineral has finished. Silicosis, asbestosis and coal workers' pneumoconiosis (CWP) are the commonest types; other examples include stannosis (from tin fume), siderosis (iron), berylliosis (beryllium) and hard metal disease (cobalt).

Silicosis

Silicosis is caused by inhalation of crystalline silicon dioxide, and affects workers in quarrying, mining, stone cutting and sandblasting. Simple nodular silicosis is the most common form and is frequently asymptomatic; more advanced types (progressive massive fibrosis (PMF)) present with increasing dyspnoea, restrictive lung function and radiographic changes of (upper lobe) nodular fibrosis (figure 1). 'Accelerated' forms also occur. Acute silicosis (causing alveolar proteinosis) results from a brief but

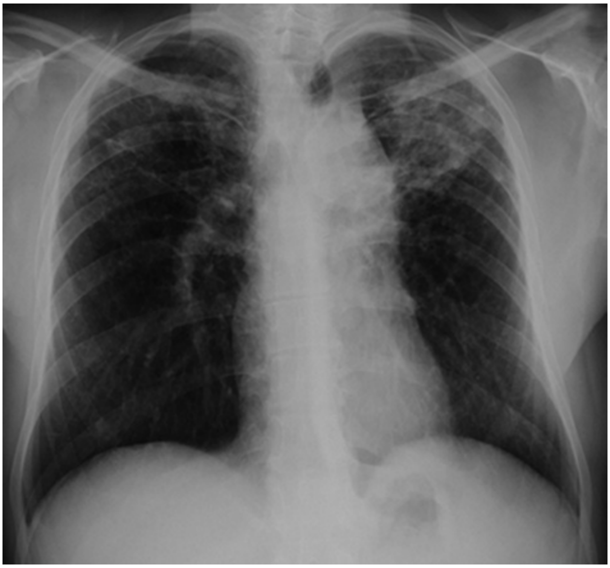


Figure 1. Chest radiograph of PMF (silicosis) in a 55-year-old stonemason.

heavy exposure: patients become intensely breathless and may die within months. Exposure to silica increases the risk of mycobacterial disease (especially TB) and of several connective tissue diseases.

Asbestosis

Asbestosis presents as a diffuse interstitial pulmonary fibrosis caused by heavy exposure to asbestos. The radiological presence of pleural thickening or plaques, indicative of exposure to asbestos, may distinguish the condition from idiopathic causes of pulmonary fibrosis.

Coal workers' pneumoconiosis

CWP is caused by inhalation of coal mine dust, a complex mixture of coal, kaolin, mica, silica and other minerals. Simple CWP usually produces no symptoms or physical signs apart from exertional dyspnoea; the diagnosis is made by the radiological presence of characteristic opacities in the context of a history of exposure. Some individuals with simple CWP develop PMF, which, when advanced, causes dyspnoea, heart failure and ultimately death.

There are no established drug treatments for pneumoconiosis. Management includes advice on further exposure; severe cases may benefit from transplantation.

Hypersensitivity pneumonitis

Numerous workplace exposures may give rise to hypersensitivity pneumonitis (HP); a careful occupational history is essential and clinicians should keep abreast of newly identified causes such as (contaminated) metal working fluid. The clinical presentation of occupational HP is variable and the familiar 'acute/chronic' classifications of the disease are not always discernible. There is good evidence that the prognosis of HP is improved if a causative allergen can be identified and eliminated.

Asbestos-related pleural diseases

Exposure to asbestos causes several pleural disorders, including pleural plaques, diffuse pleural thickening of the pleura, benign pleural effusions and malignant mesothelioma.

Lung cancer

Asbestos is the most common cause of occupational lung cancer; its effects are synergistic with smoking. There are numerous other workplace carcinogens; they give rise to a cancer that is indistinguishable from nonoccupational disease and individual attribution is very difficult.

Other airway diseases

Byssinosis arises from inhalation of cotton dust and presents with work-related airway symptoms. Obliterative bronchiolitis is a rare condition with several diverse occupational aetiologies including the manufacture of microwave popcorn and the use of glass-reinforced plastic. There is good evidence that underground coal mining can give rise to COPD, independently of smoking; other causes may include welding, grain handling and farming. Individual attribution to work is generally very difficult.

Compensation

The jurisdictions of almost all high- and middle-income countries include some form of statutory workers' compensation. Schemes vary significantly but most are based around a more-or-less closed list of prescribed occupational diseases including many respiratory examples. Clinicians should make themselves familiar with their local arrangements and advise their patients accordingly.

Further reading

- Cullinan P, *et al.* (2017). Occupational lung diseases: from old and novel exposures to effective preventive strategies. *Lancet Respir Med*; 5: 445–455.
- Perret JL, *et al.* (2017). Coal mine dust lung disease in the modern era. *Respirology*; 22: 662–670.
- Vandenplas O, *et al.* (2017). Diagnosing occupational asthma. *Clin Exp Allergy*; 47: 6–18.

Measuring the occurrence and causation of respiratory diseases

Isabella Annesi-Maesano and Riccardo Pistelli

When reduced to the simplest terms, all medical research may be defined as the study of relationships (differences or associations) between variables. A variable is any quality, constituent or characteristic of a person, animal, thing or environment that can be measured. A variable is, by definition, something that changes and the values associated with its measurements are usually grouped in a set or 'scale'. There are four basic types of scales, of which definitions and examples are reported in table 1.

Any measurement performed by using an interval or a ratio scale (continuous scales) can be translated to a category of an ordinal or nominal scale (categorical scales). For example, body temperature above or below a defined point of the Celsius or Fahrenheit scale can be used to identify subjects affected or not by fever, in this way translating from an interval to a nominal scale. Another example is the use of some values of FEV_1 to identify subjects affected by different levels of severity of COPD according to a conventional ordinal scale. In general, clinical research is mainly involved with patient-centred outcomes that are variables measured using nominal or ordinal scales (*e.g.* dichotomous variables grouping diseased or not diseased, or exposed or not exposed subjects) whereas interval or ratio scales are

Key points

- The occurrence of a health outcome is estimated by prevalence (*i.e.* the proportion of subjects affected by the health outcome in the considered population) and or incidence (*i.e.* the proportion of new cases of the health outcome in the considered population).
- The effect of exposure to a risk factor on the health outcome and the associated risk (*i.e.* the probability that the health outcome will occur following the exposure) is quantified through two measures: the ratio of the measures of disease frequency according to the presence or absence of the exposure to the factor, and the difference between these two measures.
- The existence of a statistically significant association between the exposure to a factor and the health outcome does not imply that the factor is a cause of the health outcome; causation must meet the criteria introduced by Austin Bradford Hill.
- The approach to examining the simultaneous effects of multiple exposures and, more generally, the effects of mixtures of exposures, as part of the exposome concept is recommended.

Table 1. Scales grouping measurements of health outcomes and exposure factors

Type of scale	Definition	Examples
Nominal scale	Uses names or symbols to assign each measurement to a limited number of categories that cannot be ordered one above the other	Race, sex, geographic area, diseased (yes *versus* no)
Ordinal scale	Assigns each measurement to a limited number of categories not equally spaced and ranked in a graded order	Patient status, cancer stage, COPD stage
Interval scale	Assigns each measurement to an unlimited number of categories that are equally spaced without an absolute zero point	Body temperature
Ratio scale	As the interval scale but measurements can be referred to a true zero point	Length, time, mass and all the derived physical units

more frequently used in basic research. However, clinicians should be aware of the basic methods used to study the relationships of variables measured using continuous scales, such as lung function, as well as understanding relationships of nominal or ordinal variables. The aim of this chapter is to provide basic knowledge about measures and methods commonly used to define the occurrence of clinical conditions, and to study the relationships between those variables and other variables that characterise the individual and the environment. These methods have been mainly developed for epidemiological research but they should be the landmark of any clinical reasoning. We hope to improve the skill of the readers of this book by discussing the relevance of information about the burden of diseases, as assessed by their distribution, the panel of related risk or protective factors, and the evaluation of the effectiveness of preventive measures and therapies in respiratory medicine.

Measuring occurrence of the health outcomes

Epidemiology is the study of the distribution and determinants of disease frequency in human populations. The application of this study to determine valid and precise information about the causes, preventions and treatments of disease in order to control health problems is of outstanding clinical relevance. The main goals of any epidemiological study are to measure the occurrence or frequency of health outcomes, a disease (asthma, COPD, lung cancer, *etc.*) or the intake of a medication, among others. Epidemiological studies allow also estimation of the occurrence of exposure (smoking, air pollution, occupational hazards, *etc.*). Risk, incidence proportion, and incidence and prevalence rates are popular measures of frequency. They all are proportions and rates, and their values are meaningless if the denominator is not clearly and sensibly stated. For example, imagine you read in a newspaper, reported from an important scientific journal, that men who are 40 years old have a >5% risk of developing COPD. Of course, the dimension of this risk changes according to the time interval used in the denominator: the risk is high or low according to short or long time interval. In many similar cases, the undefined denominator is the entire life span of individuals, but the reader should understand that the life span, which varies between individuals and populations, is not the best denominator to produce a broadly valid measure of risk. Unfortunately, reliable figures of risk are not available for many health problems, including many respiratory diseases.

Incidence and risk

Incidence is a measure of the risk of developing a new health condition or outcome within a specified period of time, expressed as a proportion or rate. The risk, or incidence proportion (also known as the cumulative incidence), is the number of new cases within a specified time period divided by the size of the population initially at risk, and can be expressed by the formula

$$\text{Risk} = \text{incidence proportion} = \frac{a}{N} \tag{1}$$

in which a is the number of subjects developing a health outcome out of N people followed for a time period. Of course, any particular noncommunicable disease has a very low risk over a very short time period and the cumulative risk increases with time. However, the risk may change during the lifetime of individuals. As an example, many chronic respiratory diseases are associated with ageing and their risk clearly increases from the first to the last decade of life. However, defining risk is not as simple as it may appear from equation 1. Actually, the value of N may decrease over the time period for two main reasons: the competing risk and the loss to follow-up. First, let us consider a study aiming to define the risk of death from lung cancer in a cohort of smokers (*i.e.* a group of individuals sharing a particular demographic characteristic). It is plausible that, during the follow-up period, many subjects in the cohort will die from many different diseases and not from lung cancer. However, some of these subjects may have developed lung cancer but, before clinical manifestation, die of another disease. If we include those subjects in the denominator, the ratio will give an underestimation of the true risk of death from lung cancer. Secondly, suppose that some subjects included in the cohort were lost during the follow-up period (this is usual in cohort studies in which the individuals are followed up for long periods). Those subjects may not develop the outcome we are interested in and their inclusion in the denominator will give an underestimation of risk. In conclusion, it is sensible to pay the same attention to measuring both the numerator and the denominator of a ratio.

Competing risk or loss to follow-up can be managed using a different measure of health outcome occurrence: the incidence rate expressed as the number of new cases during some time period, according to the formula

$$\text{Incidence rate} = \frac{a}{t} \tag{2}$$

in which a is the number of incident cases in the cohort, as in equation 1, and t is the total time interval experienced by the subjects followed. t is calculated by summing the time for which each subject has been at risk of developing the outcome. For events that may recur during the follow-up period, t is calculated by adding the contribution of each subject according to one of the following options: the time experienced up to the first occurrence (in this case, the numerator includes only one occurrence per subject) or all the time intervals the subject was at risk of getting any of these occurrences (in this case the numerator includes all the occurrences experienced by each subject). The exacerbation of COPD is a typical example of a recurrent event. Readers should be aware that different results may be produced by the different methods of calculating t

for this outcome and that, whichever the choice, its rationale should be clearly pre-specified in clinical trials. The interpretation of incidence rate is not as simple as for the incidence proportion. The latter is a probability and is expressed as a number in the range 0–1; however, the incidence rate may assume any value from 0 to infinity. We may represent the incidence rate as the instantaneous velocity of a vehicle and the incidence proportion as the proportion of a journey covered by the same vehicle in a defined time period. Using this representation, we may suggest that incidence rate and risk for a health outcome may be related by the formula

$$\text{Risk} = \text{incidence rate} \times t \tag{3}$$

We must remember that this formula may hold for short time intervals but not for longer intervals, during which the loss to follow-up and the competing risk will complicate the relationship between the two measures of occurrence. It is possible to find a solution to that complication by dividing a long time into shorter time intervals for which equation 3 may hold, and measuring the risk (or probability) of developing the outcome in each time interval. The overall probability will be equal to the product of probabilities of developing the outcome through all time intervals. This method is what is generally known as a survival analysis, and it can be applied to any outcome with a well-defined time of appearance during the follow-up of a cohort. In respiratory medicine, the results of many trials on chronic disease have been analysed using the survival analysis approach.

Prevalence

Prevalence is the proportion of subjects affected by a disease (or symptom or dysfunction) or, more generally, the fact of presenting a health outcome in a defined population.

It can be estimated by the number of cases within a specified time period divided by the size of the population initially at risk, and can be expressed by the formula

$$\text{Prevalence proportion} = P = \frac{n}{N} \tag{4}$$

in which n is the number of subjects developing a health outcome out of N people for a time period.

Whereas risk and incidence rate are measures of disease onset, prevalence is a measure of disease status. The value of prevalence is related not only to disease incidence but also to disease duration. The relationship of prevalence to incidence and duration of disease is expressed by the formula

$$\frac{P}{1-P} = ID \tag{5}$$

in which P is prevalence, I is incidence and D is the mean duration of the health outcome. The ratio on the left side of equation 5 is known as the prevalence odds (in general, the odds of an event happening is the ratio of the probability that it happens to the probability that it does not). For a low prevalence, equation 4 may be written as

$$P \approx ID \tag{6}$$

In this case, the prevalence proportion may be considered to approximate to the product of incidence and duration. It is clear that prevalence is a good measure of the burden of a disease and can be quite useful for public health research and decision making. However, prevalence cannot be used for causal inference about risk factors for a disease, except in some rare cases. Factors that may determine a health outcome or may increase its duration can be associated with an increased prevalence. A well-known example of this situation in respiratory medicine is offered by the prevalence studies in asthma published in recent decades. Many factors have been found to be significantly associated with an increased prevalence of asthma but, for most of them, the crucial question ‘is it a cause or a factor that increases the duration of asthma and the reporting of symptoms?’ is still open. Of course, a reliable prevalence proportion or ratio depends on both a satisfactory measurement of population and prevalent cases. Sometimes, the definition of a prevalent case for a specific health outcome may be different among studies and this may lead to quite different prevalence estimates. Prevalence studies on COPD using different clinical definitions (*e.g.* diagnosis of chronic bronchitis or emphysema) or, more recently, different cut-off values of spirometric data, are good examples of this situation. Prevalence can be used for causal inference in the case of genetic factors, as genetic background precedes the development of the disease.

Measuring the effects of exposure to risk factors

The second major goal of epidemiology is to measure the effect of exposure on the health outcome and to estimate the associated risk, *i.e.* the probability that the health outcome will occur following the exposure. This is obtained through different types of study design, according to the research question. Epidemiological study design is divided into:

- Experimental studies, which include clinical or prevention trials (field trials and community trials)
- Observational studies, which include cross-sectional studies, cohort studies, case–control studies, panel studies and crossover studies, according to the particular research question, based on individual data (table 2) and ecological data.

Study designs with individual data

In experimental studies, the investigator assigns subjects to treatments (vaccination, treatment, prevention, *etc.*) and evaluates their effectiveness, whereas in observational studies, the researcher observes subjects and waits for the outcome to happen.

Each type of study design represents a different way of harvesting data and information. In experimental studies, the study population is enrolled on the basis of eligibility criteria that reflect the purpose of the prevention or clinical trial, as well as scientific, safety, ethical and practical considerations. Scientific, safety, ethical and practical considerations are also applied in observational studies. An example of a cross-sectional study is given by the prevalence studies on asthma published in the past few decades, such as ISAAC (International Study of Asthma and Allergies in Childhood). Case–control design was used to find risk factors for lung cancer and for all the diseases with a low occurrence frequency. Cohort studies have provided proof of the cause–effect relationship between tobacco smoking and lung cancer. Another type of study is represented by the panel study. A panel study is defined as an investigation that collects information on the same individuals at different points in time. Panels of asthma patients have been involved in the study of the short-term effects of air pollution. A panel study is, therefore, a longitudinal study; it differs from other studies that collect

Table 2. Main types of epidemiological study using individual data

Type of study	Description	Type of estimation
Experimental studies		
Clinical studies	Trial in which subjects are randomly given the treatment or placebo	Effectiveness of the treatment by comparing the two groups (the treatment and control group, respectively)
Intervention studies	Inference study in which individuals receive an intervention in order to modify a supposed causal factor for disease incidence	Estimation of the effect of the intervention on the health outcome
Observational studies		
Cross-sectional studies	Descriptive study in which health outcome and exposure status are measured simultaneously in a given population Can be thought of as providing a 'snapshot' of the frequency and characteristics of health and exposure in a population at a particular point in time	Prevalence of acute or chronic health outcomes in a population Relationship between exposure and health outcome; however, since exposure and disease status are measured at the same point in time, it may not be possible to distinguish whether the exposure preceded or followed the health outcome and, thus, cause-and-effect relationships cannot be established
Cohort studies	Longitudinal investigation in which the occurrence of a particular health outcome is compared in well-defined groups of people who are alike in most ways but differ in a certain characteristic, such as (but not uniquely) an exposure Cohort studies are either retrospective (backward looking) or prospective (forward looking) In a prospective investigation, at the beginning, the individuals do not present the health outcome The prospective cohort design can establish whether having been exposed is a cause of the disease development	Incidence of health outcome Relationship between exposure and health outcomes Causal relationship (through the relative risk) in the case of prospective cohorts, provided that the Hill criteria are satisfied

(*Continued*)

Table 2. Continued

Type of study	Description	Type of estimation
Case–control studies	Investigation that compares two groups of people: those with the disease or condition under study (cases) and a very similar group of people who do not have the disease or condition (controls) Medical and lifestyle histories including exposures of the people in each group are analysed to learn what factors may be associated with the disease or condition Case–control studies are usually retrospective but they can be prospective	Relationship between the exposure and the health outcome (through the odds ratio)
Crossover studies	Investigation that compares the same individuals in the respect of a risk factor or a treatment during a retrospective or prospective follow-up	Relationship (through the relative risk) between exposure and health outcome (aggravations and exacerbations)

information over time, such as time series and cohort studies, in that it studies the same persons longitudinally. A crossover study is another type of longitudinal study in which each subject receives a sequence of different treatments (or exposures) and is a control of him/herself. While crossover studies can be observational studies, like in the investigation of the impact of air pollution on asthma or COPD aggravation, many important crossover studies are controlled experiments. Randomised, controlled crossover experiments are especially important in healthcare. A crossover trial has a repeated measures design in which each patient is assigned to a sequence of two or more treatments, one of which may be a standard treatment or a placebo. A crossover study has two advantages over both a parallel study and a non-crossover longitudinal study. First, the influence of confounding covariates is reduced because each crossover patient serves as their own control. By investigating changes of both exposure and health in a same individual, panel and crossover studies have the advantage to eliminate genetic background and confounding from individual factors (smoking, behaviour, *etc.*). Second, optimal crossover designs are statistically efficient, and so require fewer subjects than non-crossover designs (even other repeated measures designs).

Study designs with aggregated data

All the studies presented above are based on individual data for both health outcomes and exposure. Ecological studies also exist, in which the unit of analysis is a population rather than an individual. These are studies of risk-modifying factors on health outcomes based on populations defined either geographically or temporally. Both risk-modifying factors and outcomes are averaged for the populations in each geographical or temporal unit and then compared using standard statistical methods. In this case, the inference is ecological. For instance, an ecological study may look at the association between smoking and lung cancer deaths in different countries, and explore differences among them. Geographic information systems (GIS) constitute a very useful tool that improves the ability of ecological studies to be able to determine a link between health data and a source of environmental exposure using spatial information. Ecological studies are subjected to ecological fallacy to indicate that risk associations apparent between different groups of individuals may not accurately reflect the true association. This is why ecological studies should include in the analysis as many known risk-modifying factors for any health outcome as possible. In addition, the results from ecological studies should be evaluated by other methods, using, for example, Hill's criteria for causality. Ecological studies have often found links between risk-modifying factors and health outcomes well in advance of other epidemiological approaches. Therefore, they have allowed the development of hypotheses that, although providing limited information, have been useful to promote other study designs.

Quantitative assessment of the relationship between exposure and health outcome

There are two ways to quantitatively measure the effect of a given factor on the health outcome or the condition of interest: the ratio of the measures of disease frequency according to the presence or absence of the exposure to the factor, and the difference between these two measures. The ratio is the measure of the strength of the association between a factor and the health outcome, whereas the difference is an estimate of the health impact of the factor under the hypothesis that the association is of cause–effect type and of the consequences of avoiding or diminishing the exposure to the factor. Specific statistical tests are necessary to confirm the existence of an effect. In the case that both the health outcome and the exposure are dichotomous variables, their relationship can be quantified and its statistical significance can be established by organising a 2×2 (two columns and two rows) contingency table, as represented in table 3.

A visual presentation of the relationship between a factor and a health outcome when both are a dichotomous variable is shown in figure 1 where, for instance, the highest number (*a*) is observed for individuals who were exposed to the factor and presented the health outcome and the lowest (*b*) for individuals who were exposed to the factor but did not present the health outcome. In addition, the number of unexposed individuals who did not present the health outcome (*d*) is higher than the number of

Table 3. Contingency table presenting the association data from the case of exposure and disease that are dichotomous variables

	Health outcome		Total
	Yes	No	
Exposure			
Exposed	a	b	$a+b$
Not exposed	c	d	$c+d$
Total	$a+c$	$b+d$	N

a: number of individuals in the studied sample exposed to the potential risk factor who have experienced the health outcome; *b*: number of individuals exposed who have not experienced the health outcome; *c*: number of individuals unexposed who have experienced the health outcome; *d*: number of individuals unexposed who have not experienced the outcome; *N*: total number of individuals included in the study; $a+c=n$ is the total number of individuals who have experienced the health outcome; $a+c/N=n/N$ is the prevalence of the health outcome.

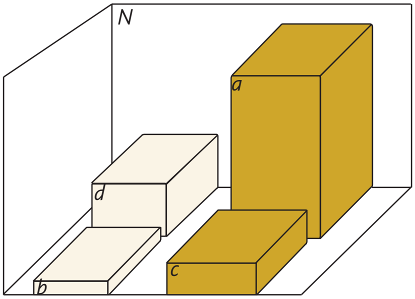


Figure 1. Distribution of the individuals according to the presence or the absence of a health outcome and exposure to a factor. a: *number of individuals in the studied sample exposed to the potential risk factor who have experienced the health outcome;* b: *number of individuals exposed who have not experienced the health outcome;* c: *number of individuals unexposed who have experienced the health outcome;* d: *number of individuals unexposed who have not experienced the outcome;* N: *total number of individuals included in the study.*

unexposed individuals presenting the health outcome (*c*). All these elements support the hypothesis that in this case there is a relationship between the exposure and the health outcome. The statistical significance of the relationship can be determined by applying statistical testing.

Ratio

In cohort studies where groups of individuals are identified on the basis of the presence or absence of exposure to a potential risk factor and then followed-up for the appearance of the health outcomes, the relative risk is used to investigate whether such a risk factor is related to the health outcome. Relative risk estimates the ratio of disease occurrence in the exposed group to that in the unexposed group. If it is not possible to find a completely unexposed group to serve as the comparison, then the least exposed group is used.

The principal measure of relative risk is the risk ratio or cumulative incidence ratio, which is the ratio of the cumulative incidence in the exposed group ($a/(a+b)$) to that in the unexposed group ($c/(c+d)$) (table 4).

Thereafter, the relative risk (RR) is given by the formula

$$\mathrm{RR} = \frac{\left(\dfrac{a}{a+b}\right)}{\left(\dfrac{c}{c+d}\right)} \tag{7}$$

RR=1 means there is no difference in risk between the two groups, RR>1 means the health event is more likely to occur in the exposed group than in the unexposed group and RR<1 means that the health event is less likely to occur in the unexposed group than in the exposed group. For RR>1, to be statistically significant, the RR has to belong to a confidence interval >1. The confidence interval is introduced due to the limitations and variables in the studied population, which in turn is due to the random errors introduced in the population's selection. Similarly, for RR<1, to be statistically significant, the RR has to belong to a confidence interval <1. The method used to calculate the 95% confidence interval for a RR is shown in appendix 1.

Table 4. Incidence of the health outcome in exposed and unexposed individuals in cohort studies

	Health outcome		Total	Incidence=risk
	Yes	No		
Exposure				
Yes	a	b	$a+b$	$\frac{a}{a+b}$ = incidence in exposed
No	c	d	$c+d$	$\frac{c}{c+d}$ = incidence in unexposed
Total	$a+c$	$b+d$	N	

a: number of individuals in the studied sample exposed to the potential risk factor who have experienced the health outcome; *b*: number of individuals exposed who have not experienced the health outcome; *c*: number of individuals unexposed who have experienced the health outcome; *d*: number of individuals unexposed who have not experienced the outcome; *N*: total number of individuals included in the study.

The case of a RR>1 with a 95% confidence interval that does not include 1 has to be interpreted as a positive association between the exposure and the health outcome at the 5% significance level, and a RR<1 with a 95% confidence interval that does not include 1 as a negative association between exposure and outcome at the 5% significance level.

In case–control studies in which the subjects are selected on the basis of disease status and the incidence of the health outcome is not available in the exposed and unexposed groups, the effect of the exposure on the health outcome is measured by the ratio of the odds of exposure among the individuals presenting the outcome to that among the individuals not presenting the outcome (the odds of the event is the quotient $p/(1-p)$, in which p is the probability in favour of the event; this value may be regarded as the relative likelihood that the event will happen). This ratio is called the odds ratio (OR) and is generally estimated as the ratio between the odds in exposed and nonexposed individuals:

$$\mathrm{OR} = \frac{\left(\dfrac{\left(\dfrac{a}{a+b}\right)}{\left(\dfrac{b}{a+b}\right)}\right)}{\left(\dfrac{\left(\dfrac{c}{c+d}\right)}{\left(\dfrac{d}{c+d}\right)}\right)} = \frac{\left(\dfrac{a}{b}\right)}{\left(\dfrac{c}{d}\right)} = \frac{ad}{bc} \qquad (8)$$

OR=1 indicates that the health event under study is equally likely to occur in both groups. OR>1 with a 95% confidence interval that does not include 1 indicates that the event is more likely to occur in the exposed group at the 5% significance level. OR<1 with a 95% confidence interval that does not include 1 indicates that the condition or event is less likely to occur in the exposed group at the 5% significance level. It can be shown that there is a mathematical relationship between the odds ratio and the relative risk:

$$\mathrm{RR} = \frac{1 - \frac{a}{a+b}}{1 - \frac{c}{c+d}} \times \mathrm{OR} \qquad (9)$$

As a consequence, when a disease is rare, *a* and *c* are small, and the odds ratio provides a valid estimate of the relative risk.

Difference

Several types of difference exist between the measures of health outcome frequency according to the presence or the absence of exposure to the factor. They include the attributable risk, preventive fraction and the population attributable risk (table 5). It must be noted that these differences have to be computed under the assumption that the factor is causally related to the health outcome, a condition encountered in prospective cohort studies, having assessed causation and disposing of the entities like incidences and relative risks necessary to compute the differences of risks. These differences can be estimated in several ways; the most used are presented in table 5.

Statistical association between exposure and health outcomes

The existence of a significant relationship between exposure and health outcome can be established independently from the estimation of the associated risk (OR, RR, *etc.*). The main statistical methods that allow the determination of the existence of a significant statistical association between a factor and the health condition of interest are indicated in appendix 2. They depend on the type of measurement scales used for the variables.

In addressing the statistical association between an exposure and the health outcome, it is important to take into account two types of error. The error of the first species (Type I error or error α) is that of wrongly concluding that a risk factor is linked to a disease, whereas the observed difference is due to the chance (fluctuations in the sampling). The general principle of statistical tests (hypothesis tests) is based on the formulation of a null hypothesis (H_o: $m_1=m_2$, equality of two means; H_o: $p_1=p_2$, equality of two proportions). The null hypothesis underlies the lack of difference between the two samples whether or not they are exposed. We try to reject H_o in favour of the alternative hypothesis (H_a: $m_1 \neq m_2$, H_a: $p_1 \neq p_2$). Rejecting the null hypothesis means accepting that there is a significant difference between the two samples, that is due to the exposure. The test result is expressed as the value of p that expresses the probability that chance accounts for a difference equal to or greater than that observed between the two means or the two proportions, which is due to the exposure. The acceptable level for error α is arbitrarily set at 5% and the value of p is usually dichotomised as ‘significant’ ($p<0.05$) or ‘not significant’ ($p \geq 0.05$). The error of the second species (Type II error or error β) is that of erroneously concluding that a risk factor is not linked to a disease, when in reality there is a difference or a link. This error is even higher when the comparison concerns smaller numbers. To reduce the error, the difference between averages or proportions must either be larger or the size of the workforce larger. In general, a risk of up to 20% ($\beta=0.20$) to miss a significant difference is taken. The power of a statistical test is the complement of the Type II error ($1-\beta$). A power of 80% ($1-\beta=0.80$) or greater is acceptable. Power expresses the probability (≥80% chance) of detecting a difference when it actually exists. It is essential to make this approach *a priori* when developing a study, by calculating the number of subjects

Table 5. Parameters estimating differences between risks

Measure	Definition	Formula
Attributable risk	The rate (excess risk) of the outcome in exposed individuals that can be attributed to the exposure Given by the difference in cumulative incidences or incidence densities of the disease in the exposed (I_E) and the unexposed individuals (I_0): $\mathbf{AR = I_E - I_0}$	$\text{AR} = \frac{a}{a+b} - \frac{c}{c+d}$
Preventive fraction	The attributable risk in the case that the exposure is preventive, so that $a/(a+b) > c/(c+d)$	$\text{PF} = \frac{\frac{c}{c+d} - \frac{a}{a+b}}{\frac{c}{c+d}}$
Attributable risk percentage or aetiological fraction	The attributable risk divided by the rate of disease among the exposed	$\text{AR\%} = \frac{\text{AR}}{\left(\frac{a}{a+b}\right)} \times 100$ $= \frac{\text{RR}-1}{\text{RR}} \times 100$
Population attributable risk	The incidence of a disease in a population that is attributable to the exposure Given by the difference between the rate of the disease in the entire population (I_{TOT}) and I_0: $\mathbf{PAR = I_{TOT} - I_0}$ or by multiplying the product of the attributable risk by the proportion of exposed individuals in the population (P_E): $\mathbf{PAR = AR \times P_E}$	$\text{PAR} = \frac{a+c}{a+b+c+d} - \frac{c}{c+d}$ $= \text{AR} \times \frac{a}{a+c}$
Combined PAR	The PAR for a combination of risk factors is the proportion of the disease that can be attributed to any of the risk factors studied	$\text{Combined PAR}^{\#} = 1 - (1 - \text{PAR}_1)(1 - \text{PAR}_2)(1 - \text{PAR}_3)\ldots$

a: number of individuals in the studied sample exposed to the potential risk factor who have experienced the health outcome; *b*: number of individuals exposed who have not experienced the health outcome; *c*: number of individuals unexposed who have experienced the health outcome; *d*: number of individuals unexposed who have not experienced the outcome. $^{\#}$: when there is no multiplicative interaction (no departure from multiplicative scale), combined PAR can be manually calculated by this formula.

necessary to include in each group to obtain the desired minimum power. However, sometimes, the power is computed *a posteriori*, to better interpret the results. Indeed, if a result is not significant, power calculation can show, that given that the sample size, the power is not enough. It will be an explanation of why result is not significant. In addition, the confidence interval of the estimation of the association (OR, RR, *etc.*) will indicate the range of values that are consistent with the data. Confidence intervals are almost always more informative than significance tests.

Causation

The existence of a statistically significant association between the exposure to a factor and the health outcome does not imply that the factor is a cause of the health outcome. Assessing causation implies several criteria introduced by Austin Bradford Hill (table 6). Notably, none of the proposed criteria can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required *sine qua non*.

Introducing the exposome

Establishing causation is even more difficult in the case of multifactorial diseases, which need the introduction of the exposome concept. The exposome constitutes the totality of environmental factors to which an individual is exposed from prenatal

Table 6. Criteria for assessing evidence of causation

1	**Strength** The larger the association, the more likely that it is causal However, a small association does not mean that there is not a causal effect
2	**Consistency** Consistent findings observed by different persons in different places with different samples strengthen the likelihood of an effect
3	**Specificity** The more specific an association between a factor and an effect, the greater the probability of a causal relationship Causation is likely in case of a very specific population at a specific site and disease with no other likely explanation.
4	**Temporality** The effect has to occur after the cause
5	**Biological gradient** Greater exposure should generally lead to greater incidence of the outcome
6	**Plausibility** A plausible mechanism between cause and effect is helpful although, very often, knowledge of the mechanism is limited
7	**Coherence** Coherence between epidemiological and laboratory findings increases the likelihood of an effect of the exposure on the health outcome Notably, sometimes we lack such laboratory evidence
8	**Experiment** ‘Occasionally it is possible to appeal to experimental…evidence’
9	**Analogy** The effect of similar factors may be considered

Information from Hill (1965).

life (since we now know the role of the environment on the fetus as being related to the subsequent risk of development of certain characteristics or diseases) to death. Dealing with several factors simultaneously requires sophisticated statistical tools and resources.

Bias and errors

Occurrence of health outcomes and exposure, and measures of associations and causation are challenged by biases and errors. Random error corresponds to imprecision and bias to inaccuracy. Error is defined as the difference between the true value of a measurement and the recorded value of a measurement. There are many sources of error in collecting clinical data. Error can be described as random or systematic. Random error is also known as variability, random variation or 'noise in the system'. Heterogeneity in the human population leads to relatively large random variation in clinical trials. Random error has no preferred direction, so we expect that averaging over a large number of observations will yield a net effect of zero. The estimate may be imprecise but not inaccurate. The impact of random error, imprecision, can be minimised with large sample sizes. Systematic error, or bias, refers to deviations that are not due to chance alone. There are several types of bias. Among the most important are:

- Recall bias
- Selection bias
- Information bias
- Confounding

Recall, selection and information bias can be reduced by good protocol. Confounding occurs when a variable is associated with both the exposure and the health outcome that we are studying. When the effect of an exposure is mixed with the effect of another variable (the confounding variable), we may incorrectly conclude that the disease is caused by the exposure. We might then attempt to eliminate the exposure in the hope that the disease could be prevented. If, however, the association between the exposure and the disease is due to confounding and is not causal, elimination of the exposure will have no effect on the incidence of the disease. The existence of confounding variables in smoking studies made it difficult to establish a clear causal link between active smoking and lung cancer, until appropriate methods were used to adjust for the effect of the confounders. An example of confounding variable in the relationship between active smoking and lung cancer is air pollution, which can cause cancer and is also associated with the exposure of interest, smoking. The effect of a confounder can be taken into account by adjusting for it with an appropriate statistical model or matching individuals according to it.

Bias has a net direction and magnitude so averaging over a large number of observations does not eliminate its effect. In fact, bias can be large enough to invalidate any conclusion. Increasing the sample size will not eliminate all bias. In epidemiological and clinical studies, bias can be subtle and difficult to detect. A study can be invalidated by the presence of bias. Thus, the design of clinical or epidemiological trials has to focus on removing known biases. Another important element to be introduced in epidemiological investigations is the effect modifier, a factor that modifies the effect of a putative causal factor under study. Effect modification (also known as statistical interaction) occurs when the effect measure depends on the level of another factor. For example, bacille Calmette–Guérin (BCG) immunisation is an effect modifier for the consequences of exposure to *Mycobacterium tuberculosis* and has to be taken into account when investigating risk factors for TB. Effect modification is detected by varying the selected effect measure for the factor under study across levels of the other factor. In this example, the modification effect of BCG immunisation could be estimated by computing the odds ratio between tobacco smoking and TB according to the presence or absence of BCG immunisation. The effect of a modifier can be taken into account through matching individuals according to different levels of the modifier (stratification).

Sensitivity and specificity

Sensitivity is the probability that the criterion used to define the case will produce a true positive result when used in a population (compared to a reference or 'gold standard'). Specificity is the probability that the criterion will produce a true negative result when used (as determined by a reference or 'gold standard'). Using a contingence table relating reference and new criterion results (table 7), the following formulae are obtained for sensitivity and specificity:

$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}} \tag{10}$$

$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}} \tag{11}$$

where TP is the number of true positive specimens, FP is the number of false positive specimens, FN is the number of false negative specimens and TN is the number of true negative specimens. An example of an application for sensitivity and specificity calculation is in the validation of biomarkers of exposure or effects. Sensitivity and specificity are characteristics of the test. The population does not affect the results.

Another possible question concerns the probability that a person with a positive test truly has the disease or is truly exposed. This can be answered introducing the positive predictive value (PPV) and the negative positive value (NPV). PPV is the probability that following a positive test result, the individual will truly have that specific disease or that exposure. NPV is the probability that following a negative test result, that individual will truly not have that specific disease or exposure. Using a contingence table relating reference and new criterion results (table 7), the following formulae are obtained for PPV and NPV.

$$\text{PPV} = \frac{\text{TP}}{\text{TP} + \text{FP}} \tag{12}$$

Table 7. Sensitivity and specificity computation

New criterion results	Reference criterion results	
	Positive	Negative
Positive	TP	FP
Negative	FN	TN

TP: number of true positive specimens; FP: number of false positive specimens; FN: number of false negative specimens; TN: number of true negative specimens.

$$\text{NPV} = \frac{\text{TN}}{\text{TN} + \text{FN}} \qquad (13)$$

Positive and negative predictive values are influenced by the prevalence of disease in the population that is being tested. In a high-prevalence setting, it is more likely that persons who test positive truly have disease than if the test is performed in a population with low prevalence.

Conclusion

Epidemiology provides methods for measuring the occurrence and the causation of respiratory diseases. In assessing occurrence and relationships between exposure and health outcomes, criteria of relevance should include:

- The representativeness of the studied samples particularly in studies with samples of the general population
- Clear definitions of both the health outcome (or dependent variables) and the exposure (or independent variables) to be included in the models

Further reading

- Hill AB (1965). The environment and disease: association or causation? *Proc R Soc Med*; 58: 295–300.
- Rothman KJ. (2012). Epidemiology: An Introduction. 2nd Edn. New York, Oxford University Press.
- Swinscow TDV, *et al*. (2009). Statistics at Square One. 11th Edn. London, BMJ Books.
- Swinscow TDV, *et al*. (2006). Statistics at Square Two. 2nd Edn. London, BMJ Books.

Suggested free software

- Epi Info. Version 7.2.3 (May 30 2019). Atlanta, Centers for Disease Control and Prevention, 2019. Available from: wwwn.cdc.gov/epiinfo/

Appendix 1: 95% confidence intervals for the relative risk and the odds ratio

Given the 2×2 contingency table relating exposure to health outcome, a common way to calculate the 95% confidence interval is as follows.

In the case of the relative risk (approximate estimate):

$$\text{Upper limit} = e^{\text{logRR}+1.96\times\sqrt{}\text{vlnRR}} \qquad (14)$$

$$\text{Lower limit} = e^{\text{logRR}-1.96\times\sqrt{}\text{vlnRR}} \qquad (15)$$

where √vlnRR represents the square root of the natural log of the risk ratio, defined as

$$\text{lnRR} = \log\left(\frac{\left(\frac{a}{a+b}\right)}{\left(\frac{c}{c+d}\right)}\right) \qquad (16)$$

which is asymptotically normal with variance

$$\mathrm{vlnRR} = \frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d} \qquad (17)$$

When there are zeros, a common convention is to add 1/2 to each cell.

In the case of the odds ratio:

$$\text{Upper limit lnOR} = \text{lnOR} + 1.96 \times \textsc{se}(\text{lnOR}) \qquad (18)$$

$$\text{Lower limit lnOR} = \text{lnOR} - 1.96 \times \textsc{se}(\text{lnOR}) \qquad (19)$$

which become

$$\text{Upper limit OR} = e^{\text{upper limit lnOR}} \qquad (20)$$

$$\text{Lower limit OR} = e^{\text{lower limit lnOR}} \qquad (21)$$

where SE(lnOR) is the standard error of the natural log of the odds ratio, which is the variance of lnOR), calculated as $(1/a)+(1/b)+(1/c)+(1/d)$.

Appendix 2: Main methods used to assess the relationship between exposure and health outcome

We have presented how to assess the relationship between the health outcome and exposure in the case where both variables are dichotomous. Table 8 introduces main methods that can be used in other cases.

Table 8. Main statistical methods for assessing the relationship between health outcomes and exposures

Statistical methods	Description
Correlation	A single number that describes the degree of relationship between two continuous variables
ANOVA	A statistical test of whether or not the means of several groups are all equal (*i.e.* are not statistically significantly different)
Chi-squared	A statistical test to compare two variables in a contingency table to see if they are related; in a more general sense, it tests to see whether distributions of categorical variables differ from each another
Linear regression	Approach to modelling the relationship between a continuous variable *y* and one or more variables *x* that may be either continuous or categorical taking into account confounders

(*Continued*)

Table 8. Continued

Statistical methods	Description
Logistic regression model	Approach to predicting the probability of occurrence of an event by fitting data to a logit function Makes use of several predictor variables that may be either continuous or categorical Usually used to estimate the odds ratio between the exposure and the health outcome after adjustment for potential confounders
Cox proportional hazards model	Approach to investigating the association between the occurrence time of a health outcome (death, abortion, *etc.*) and one or more predictor variables taking confounders into account
Environment-wide association study (EWAS) Two-step Environment-wide Association Study (EWAS2); Deletion/substitution/addition (DSA) algorithm; Least absolute shrinkage and selection operator (LASSO); Group-lasso INTERaction-NET, *etc.*	Approach to examining the simultaneous effects of multiple exposures and, more generally, the effects of mixtures of exposures, as part of the exposome concept

Indoor and outdoor pollution

Giovanni Viegi, Marzia Simoni, Sara Maio and Sandra Baldacci

Air pollution is a well-established hazard to human health. Air quality is particularly important for subpopulations that are more susceptible (*i.e.* children, the elderly, subjects with cardiorespiratory diseases or those who are socioeconomically deprived) or at higher risk of specific exposures (workers exposed to inorganic dust, wood dust, fumes, gases and cleaning agents). Children are particularly vulnerable since they inhale a higher volume of air per body weight than adults, their lungs are growing, their immune system is incomplete and defence mechanisms are still evolving. Air pollution can affect the cells in the lung by damaging those that are most susceptible and, if the damaged cells are important in the development of new functional parts of the lung, the lung may not achieve its full growth and function as a child matures to adulthood. This can lead to enhanced susceptibility during adulthood to the effects of ageing and infections, as well as to pollutants. Air pollution has both short-term (peak exposures) and long-term adverse effects, which can involve not only the pulmonary system but also the cardiovascular system.

Air pollution is mostly produced by human activities. Other pollutants derive from natural sources, such as biological allergens (*e.g.* house dust mites, pet dander and moulds) and natural phenomena (*e.g.* volcanic activity, desert dust storms and forest fires).

Recent research focuses on two broad sources:

- Motor vehicles and industrial plants
- Biomass fuels

Key points

- Recent epidemiological studies have clearly shown that outdoor and indoor air pollution affects respiratory health worldwide, causing an increase in the prevalence of cardiovascular and respiratory symptoms/diseases (*i.e.* COPD, asthma, hay fever and lung function reduction) and of mortality, both in children and in adults.
- Rapid industrialisation and urbanisation have increased air pollution and, consequently, the number of exposed people.
- Estimates show that ~4 million deaths per year could be attributed to indoor air pollution in developing countries.
- The abatement of the main risk factors for respiratory diseases, and the support of healthcare providers and the general community for public health policies improving outdoor/indoor air quality can achieve huge health benefits.

Traffic-related air pollution is a growing concern in both developed and less-developed countries, and industrial smokestacks continue to be a major source of outdoor air pollution from the burning of fossil fuels throughout the world. However, the most threatened populations live in developing and poor countries, where air pollution reflects a combination of traditional and modern factors. Rapid industrialisation, urbanisation and growth in vehicle use increase outdoor air pollution, and, at the same time, traditional indoor burning of solid fuels, such as coal and dung, is still widespread.

In the 2013 European 'Year of Air', the European Respiratory Society Environment and Health Committee developed 10 concise principles for clean air that summarise the scientific state of the art and provide guidance, whilst the European Union (EU) adopted a Clean Air Policy Package, including a Clean Air Programme for Europe setting objectives for 2020 and 2030, and accompanying legislative measures. Thereafter, in 2018, the European Commission adopted a communication (A Europe that Protects: Clean Air for All) that provides measures aiming to help EU Member States to combat air pollution.

Outdoor pollution

The most important outdoor pollutants derive from fossil fuel combustion. Primary pollutants directly emitted into the atmosphere are carbon monoxide, sulfur dioxide, nitrogen dioxide and particulates. Ozone is a secondary pollutant, mainly produced by chemical reaction of nitrogen dioxide and hydrocarbons in the presence of sunlight at warm temperatures. As mentioned, rapid industrialisation and urbanisation in many parts of the world have increased air pollution and, consequently, the number of people exposed to it. The Global Burden of Diseases Study 2015 showed that ambient particulate matter with an aerodynamic diameter <2.5 µm ($PM_{2.5}$) was the fifth-ranking mortality risk factor in 2015. Exposure to $PM_{2.5}$ caused 4.2 million deaths and 103.1 million disability-adjusted life-years (DALYs), representing 7.6% of total global deaths and 4.2% of global DALYs, 59% of these in East and South Asia.

Today, it is recognised that global warming will increase the effects of outdoor air pollution on health: it will lead to more frequent heat waves, during which air pollution concentrations are also elevated, and during which hot temperatures and air pollutants act in synergy to produce more serious health effects than expected from heat or pollution alone.

The main effects of the more common outdoor pollutants are summarised in table 1.

Exposure–response relationships for outdoor pollutants, especially particulates, have been confirmed by epidemiological studies in recent decades. Short-term exposure, due to acute increase in air pollution, may cause premature mortality and increase hospital admissions for exacerbations of COPD or asthma. Long-term cumulative health effects of chronic exposure comprise an increase in mortality and morbidity for cardiovascular and respiratory diseases, including COPD and lung cancer, and impaired development of the lungs in children. In COPD patients, continued exposure to noxious agents promotes a more rapid decline in lung function and increases the risk of repeated exacerbations. Air pollution can harm the fetus if the mother is exposed to high levels during pregnancy (*i.e.* intrauterine growth retardation) and can increase respiratory neonatal mortality. Particulates, nitrogen dioxide and ozone are the most important pollutants today. The health effects of particulates are more serious for fine ($PM_{2.5}$) and ultrafine ($PM_{0.1}$) particles, as they penetrate deeper into the airways of the respiratory tract, reaching the alveoli. Vehicular exhausts are responsible for small-sized airborne particulate air pollution in urban areas. Recently, much research

Table 1. Major outdoor/indoor pollutants and related health effects

Pollutant	Major sources	Health effects
Particulate matter	Outdoor Vehicular traffic Organic matter and fossil fuel combustion Power stations/industry Windblown dust from roadways, agriculture and construction Bushfires/dust storms Indoor Woodstoves Organic matter and fossil fuel combustion for heating/cooking ETS	Lung cancer Premature death Mortality for cardiorespiratory diseases Reduced lung function Lower airway inflammation Upper airways irritation Neurological, cardiovascular diseases, metabolic disorders
Nitrogen dioxide	Outdoor Vehicular traffic Power stations/industry Indoor Unvented gas/kerosene appliances	Exacerbation of asthma Airway inflammation Bronchial hyperresponsiveness Increased susceptibility to respiratory infection Reduced lung function
Ozone	Outdoor Sunlight chemical reaction with other pollutants Vehicular traffic Power stations/industry Consumer products	Lung tissue damage Reduced lung function Reduced exercise capacity Exacerbation of asthma Upper airway and eye irritation
Carbon monoxide	Outdoor Organic matter and fossil fuel combustion Vehicular traffic Domestic heating Indoor Organic matter and fossil fuel combustion for heating/cooking Woodstoves Unvented gas/kerosene appliances ETS	Death/coma at very high levels Headache, nausea, breathlessness, confusion/reduced mental alertness Low birth weight (fetal exposure)
Sulfur dioxide	Outdoor Coal/oil-burning power stations Industry/refineries Diesel engines Metal smelting	Exacerbation of respiratory diseases including asthma Respiratory tract irritation

(*Continued*)

Table 1. Continued

Pollutant	Major sources	Health effects
VOCs	Indoor	Lung cancer
	Building materials and products such as new furniture, solvents, paint, adhesives, insulation Cleaning activities and products Materials for offices	Asthma, dizziness, respiratory and lung diseases Chronic eye, lung or skin irritation Neurological and reproductive disorders

has pointed out the negative effects of diesel exhaust exposure; people are exposed not only to motor vehicle exhausts but also to exhausts from other diesel engines (*e.g.* diesel trains and ships) and from power generators. In June 2012, the International Agency for Research on Cancer (IARC) classified diesel engine exhaust as carcinogenic to humans (Group 1) based on sufficient evidence that exposure is associated with an increased risk of lung cancer.

The role of air pollution in the epidemics of allergies is still debated, even if experimental studies have suggested that the effects of air pollutants on the development and worsening of allergies are biologically plausible. Asthma shows a strong familial association but genetic factors alone are unlikely to account for the rapid rise in its prevalence seen in recent decades. The rapid increase in the burden of atopic diseases occurred along with rapid urbanisation/industrialisation. Thus, genetic and environmental factors may interact to cause asthma. A growing number of studies shows significant associations of traffic with new-onset asthma, or asthma symptoms/exacerbations, in children.

Moreover, recent evidence shows associations between outdoor air pollution and systemic or metabolic effects involving multiple pathophysiological pathways, like type 2 diabetes, birthweight and prematurity, and neurological and psychiatric outcomes.

Some recent studies confirming the association between urban air pollution and health status are described here.

- The Italian EpiAir project, performed in 25 cities on subjects aged ≥35 years, highlighted an increase in mortality from respiratory diseases of 1.67% (95% CI 0.23–3.13%) for a 10-$\mu g \cdot m^{-3}$ increase in nitrogen dioxide, and an increase in urgent hospital admissions from respiratory diseases of 1.23% (95% CI 0.58–1.88%) for a 10-$\mu g \cdot m^{-3}$ increase in $PM_{2.5}$ and of 1.29% (95% CI 0.52–2.06%) for a 10-$\mu g \cdot m^{-3}$ increase in nitrogen dioxide.
- Data from a UK study showed that 38% of annual childhood asthma new cases may be attributable to air pollution; a range from 6% to 12% may be specifically attributable to traffic-related air pollution.
- Our team in Pisa, Italy, has reported that people living in an urban area are at higher risk of having increased bronchial responsiveness (OR 1.41, 95% CI 1.13–1.76) than people living in a rural area. Moreover, we showed long-term effects of the exposure to traffic air pollution: people residing near a major road (within 100 m) showed significantly higher risks (OR ranging from 1.61 to 2.07) of persistent wheezing, dyspnoea, attacks of shortness of breath with wheezing, asthma, COPD, airway obstruction and atopy; and people living in a urban area, with respect to a suburban area, had higher risks of allergic rhinitis (OR 1.19), phlegm (OR 1.30) and

COPD (OR 1.54). Another Italian study, performed on children (aged 10–17 years) living in Palermo, confirmed the negative impact of heavy traffic exposure, showing significantly higher risks (OR ranging from 1.39 to 1.84) of asthma, rhinoconjunctivitis and reduced lung function.

Indoor pollution

Indoor environments contribute significantly to human exposure to air pollutants. People spend most of their time indoors: up to 90% in industrialised countries. Furthermore, levels of some pollutants are higher inside than outside buildings. Even at low concentrations, indoor pollutants may have an important biological impact because of long exposure periods (*e.g.* at home or school and in workplaces). Globally, 4.3 million deaths were attributable to household air pollution (HAP) in 2012, almost all in low- and middle-income countries. The large increase in burden compared with the previous estimate of 2 million deaths from HAP is mainly due to having included additional health outcomes (*e.g.* cerebrovascular/ischaemic heart diseases), additional evidence and an increase in noncommunicable diseases. Globally, 30% of COPD deaths are attributable to household air pollution. There is consistent evidence that exposure to indoor pollutants increases the risk of several respiratory/allergic symptoms and diseases (table 1).

Relevant indoor pollution sources are: environmental tobacco smoke (ETS), a common source of indoor particulates; biomass (wood/coal) fuel use; and mould/damp. Furthermore, in western countries and in societies that adopt western lifestyles, consumer products (*i.e.* computers, televisions and synthetic building materials) emit large quantities of volatile organic compounds (VOCs) and nonorganic compounds.

ETS is associated with increased risk of acute respiratory or irritation symptoms, infectious diseases, chronic respiratory illnesses, lung function reduction and even lung cancer. In children, ETS also increases the risk of sudden infant death syndrome, middle-ear disease, lower respiratory tract illnesses, wheeze and cough. ETS exposure exacerbates pre-existing asthma, and increases symptom burden and morbidity: the largest effects are on asthma severity, after pulmonary physiology and rhinitis severity. In nonsmokers, the mortality risk for respiratory diseases is about double for those living with smokers than for those who do not. Studies performed worldwide suggest higher risk for ETS exposure in females than in males. Table 2 shows the results of meta-analyses regarding the associations of ETS exposure with respiratory symptoms/diseases.

The electronic cigarette (e-cigarette) has recently become popular around the world. People exposed to vapours from e-cigarette users are exposed to numerous pollutants above background levels, in concentrations that are associated with potential adverse health effects. Although the risk from being passively exposed to e-cigarettes is likely to be lower than that from passive exposure to conventional cigarette smoke, and more research is required, current evidence shows the potential for health impacts due to passive exposure to e-cigarette vapours. Recent discussion has focused on another form of exposure to tobacco, third-hand smoke, consisting of residual pollutants from cigarette smoke that remain in indoor environments, potentially causing adverse health effects.

About half of the world's population burns biomass for cooking, heating and lighting, in open fires or with inefficient stoves, and in poorly ventilated rooms, especially in developing countries. Biomass combustion is increasing, especially in winter, in the developed world too. Indoor air pollution from biomass fuels is strongly poverty-

Table 2 Associations between ETS exposure and respiratory symptoms/disease in never-smokers

	Population	Estimated pooled risk
Lower respiratory tract infection	<2 years of age	OR 1.55 (95% CI 1.42–1.69)
	2–6 years of age	OR 1.71 (95% CI 1.33–2.20)
Cough	Males	OR 1.60 (95% CI 1.22–2.10)
	Females	OR 1.68 (95% CI 1.17–2.34)
Asthma onset	Children	OR 1.32 (95% CI 1.24–1.41)
	Adults	OR 1.97 (95% CI 1.19–3.25)
Lung cancer	Adults	OR 1.21 (95% CI 1.13–1.30)
	Females	RR 1.27 (95% CI 1.17–1.37)
	North America	RR 1.15 (95% CI 1.03–1.28)
	Asia	RR 1.31 (95% CI 1.16–1.48)
	Europe	RR 1.31 (95% CI 1.24–1.52)

OR: odds ratio; RR: relative risk.

related and represents an important risk factor for acute respiratory illness morbidity and mortality in low-income countries, especially in children and women. In China, indoor air pollution from solid fuel use is responsible for ~420000 premature deaths annually, more than the nearly 300000 attributed to urban outdoor air pollution in the country. A more recent study raises the estimate of the death toll in China due to household air pollution to 1 million, close to the 1.2 million due to outdoor air pollution. The evidence that biomass use increases the risk of COPD in females and acute respiratory infections in children is very strong (about three-fold and over three-fold higher risk in those exposed than in the unexposed, respectively).

The IARC has classified the indoor combustion of coal emissions as Group 1, a known carcinogen to humans. There is strong evidence (moderate for males) that females exposed to smoke from coal fires in the home have an elevated risk of lung cancer (OR 1.9, 95% CI 1.1–3.5).

Based on meta-analyses, building dampness and mould are associated with approximately 30–50% increases in respiratory and asthma-related health outcomes. In children, a population attributable risk for asthma of 6.7% has been estimated. In adults, a pooled risk of cough due to indoor mould/dampness was estimated with an odds ratio of 2.10 (95% CI 1.27–3.47). There is also evidence for an association of mould exposure with new-onset asthma and worsening of pre-existing asthma (wheezing, cough and shortness of breath) in both children and adults. Allergic symptoms are commonly related to mould exposure (sneezing; nose, mouth or throat irritations; nasal stuffiness or runny nose; and red, itchy or watery eyes).

Finally, exposure to VOCs may result in a spectrum of illnesses ranging from mild (irritations) to very severe effects, including cancer. Such exposure increases the risk of respiratory/allergic effects in infants/children, like asthma, wheeze, chronic bronchitis, reduced lung function, atopy and severity of sensitisation, rhinitis, and pulmonary infections. Many studies indicate that the effects are related to very low levels of exposure. VOC exposure also seems a significant risk factor for asthma (OR ranging from 1.2 to 2.9). Many of the effects observed in children have been shown also in adults.

Biological mechanisms

Many recent studies have shown that oxidative stress induced by air pollutants plays a central role in the impact of air pollution. The first contact of inhaled ambient pollutants is with the fluid layer that covers the respiratory epithelium and the responses following the exposure are mediated through oxidation reactions occurring within this fluid air–lung interface. These reactions can result in oxidative stress and consequent increased production of inflammatory mediators from human airway epithelial cells. Oxidative stress is a situation in which the oxidant–antioxidant balance is disturbed. This imbalance can occur when the generation of oxidant molecules (free radicals) exceeds the available antioxidant defences. The consequence of this oxidative stress can be systemic or local inflammations thus involving the cardiopulmonary system.

The three most frequent pollutants causing oxidative stress include nitric oxide, which is a free radical, PM10, and ozone. The majority of human genetic association studies of air pollutants have examined ozone exposure. Ozone is a powerful oxidant and reacts with the bronchial epithelium lining fluid to generate free radicals. It depletes levels of protective antioxidants and increases the production of inflammatory mediators.

The size and the surface of particulates determine the potential to elicit oxidative damage. In general, the smaller the size of the particulates, the higher the toxicity through mechanisms of oxidative stress and inflammation. Nanoparticles (ultrafine particles with diameter <100 nm) are more toxic and inflammogenic than fine particles. They generate reactive oxygen species to a greater extent, and exacerbate pre-existing respiratory and cardiovascular disease, also through a dose–response effect.

Pulmonary impairment related to pollutant exposure may be higher in individuals who are genetically at risk of higher susceptibility to oxidative stress. The formation of reactive oxygen species is an important aspect of the inflammatory process of asthma and genetic aberrations associated with antioxidants might explain the reason why some people with asthma seem at higher risk of exacerbations due to air pollution exposure.

Conclusion

Outdoor and indoor pollution greatly affect respiratory health worldwide, as shown by many recent epidemiological studies. Patient education about the importance of good indoor air quality in the home and workplace is essential. The support of healthcare providers and the general community for public health policy aimed at improving outdoor air quality through programmes for abating/reducing pollutant emissions is also important. Moreover, there is evidence that increased antioxidant intake may protect against the effects of air pollution. The role of the physician is essential in patient education on the preventive actions to reduce health effects due to pollution. Hopefully, these actions will reduce the negative effects of air pollution on the respiratory health status and quality of life of the general population, particularly of more susceptible individuals.

Further reading

- Baldacci S, *et al.* (2015). Allergy and asthma: Effects of the exposure to particulate matter and biological allergens. *Respir Med*; 109: 1089–1104.
- Bentayeb M, *et al.* (2015). Indoor air quality, ventilation and respiratory health in elderly residents living in nursing homes in Europe. *Eur Respir J*; 45: 1228–1238.

- Brunekreef B, *et al.* (2012). Ten principles for clean air. *Eur Respir J*; 39: 525–528.
- Cibella F, *et al.* (2011). Proportional Venn diagram and determinants of allergic respiratory diseases in Italian adolescents. *Pediatr Allergy Immunol*; 22: 60–68.
- Cibella F, *et al.* (2015). Effect of indoor nitrogen dioxide on lung function in urban environment. *Environ Res*; 138: 8–16.
- Cohen AJ (2017). Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet*; 389: 1907–1918.
- Ferkol TW, *et al.* (2018). Electronic cigarette use in youths: a position statement of the Forum of International Respiratory Societies. *Eur Respir J*; 51: 1800278.
- Hulin M, *et al.* (2012). Respiratory health and indoor air pollutants based on quantitative exposure assessments. *Eur Respir J*; 40: 1033–1045.
- International Agency for Research on Cancer (2012). Diesel engine exhaust carcinogenic. www.iarc.fr/en/media-centre/pr/2012/pdfs/pr213_E.pdf
- Künzli N, *et al.* (2010). Air quality and health. https://www.ersnet.org/publications/air-quality-and-health
- Landrigan PJ, *et al.* (2018). The Lancet Commission on pollution and health. *Lancet*; 391: 462–512.
- Maio S, *et al.* (2016). Respiratory symptoms/diseases prevalence is still increasing: a 25-yr population study. *Respir Med*; 110: 58–65.
- McGwin G, *et al.* (2010). Formaldehyde exposure and asthma in children: a systematic review. *Environ Health Perspect*; 118: 313–317.
- Nuvolone D, *et al.* (2011). Geographical information system and environmental epidemiology: a cross-sectional spatial analysis of the effects of traffic-related air pollution on population respiratory health. *Environ Health*; 10: 12–23.
- Öberg M, *et al.* (2010). Second-hand smoke: assessing the environmental burden of disease at national and local levels. Geneva, World Health Organization.
- Thurston GD, *et al.* (2017). A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework. *Eur Respir J*; 49: 1600419.
- Viegi G, *et al.* (2004). Indoor air pollution and airway disease. *Int J Tuberc Lung Dis*; 8: 1401–1415.
- World Health Organization (2012). Burden of disease from Household Air Pollution for 2012. http://www.who.int/phe/health_topics/outdoorair/databases/en/
- World Health Organization (2009). WHO guidelines for indoor air quality: dampness and mould. www.euro.who.int/__data/assets/pdf_file/0017/43325/E92645.pdf
- Yang W, *et al.* (2009). Air pollutants, oxidative stress and human health. *Mutat Res*; 674: 45–54.

High altitude and diving-related diseases

Yvonne Nussbaumer and Konrad E. Bloch

The pressure changes associated with increasing altitude and depth exert a unique effect on human physiology. Pressure changes experienced during diving greatly exceed those experienced at altitude. The barometric pressure at the summit of Mount Everest (8848 m) is approximately one-third (253 mmHg) of the sea level value (760 mmHg). Ambient pressure increases linearly with the depth of water submergence (1 additional bar (750 mmHg) for each 10 m of sea water), resulting in a four-fold pressure increase to approximately 3040 mmHg (404 kPa) at 30 m below sea level.

High altitude-related diseases

Physiological response to altitude

The low barometric pressure experienced at altitude reduces inspiratory and arterial oxygen partial pressure. The immediate physiological response is a rise in heart rate and pulmonary arterial pressure, and chemoreceptor-mediated hyperventilation. It tends to mitigate hypoxaemia but the associated hypocapnia, with P_{aCO_2} close to the apnoeic threshold (figure 1), promotes ventilatory instability with periods of hyperpnoea alternating with central apnoea/hypopnoea. This pattern, called "high altitude periodic breathing", is seen in healthy subjects at altitudes of >1600 m, mostly during sleep. It may cause intermittent dyspnoea and sleep disturbances. Prolonged altitude exposure triggers acclimatisation mechanisms, including an increased

Key points

- Acute, altitude-related illnesses include: acute mountain sickness; high-altitude pulmonary oedema; high-altitude cerebral oedema.
- Prevention measures in mountain tourists include: a moderate ascent rate; a low sleeping altitude; avoidance of heavy exertion; treatment with acetazolamide or dexamethasone.
- Elevated environmental pressure during scuba-diving imposes an excessive load on the respiratory system.
- Uncontrolled, rapid assent puts scuba divers at risk of barotrauma, as well as serious neurological and muscular-skeletal complications.
- Essential treatments for decompression sickness include: immediate 100% oxygen breathing; volume repletion; timely hyperbaric oxygen therapy.

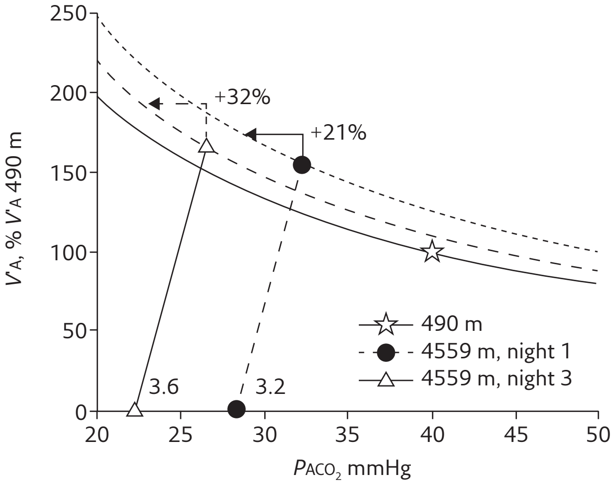


Figure 1. Mechanisms of periodic breathing at high altitude: mean alveolar ventilation (V'_A) versus *alveolar carbon dioxide tension* (P_{ACO_2})*. In the isometabolic lines for mountaineers ascending from 490 m to 4559 m,* P_{ACO_2} *is represented by end-tidal* P_{CO_2} *as a surrogate. The eupneic* P_{CO_2} *(represented by the symbols on the lines) dropped from 40 mmHg at 490 m to 32 and 26 mmHg, respectively, in the 1st and 3rd nights at 4559 m. This was associated with a decrease in the corresponding apnoea threshold, the* P_{aCO_2} *at* $V'_A = 0$*, from 28 to 22 mmHg. The increase in the slope of the line connecting the eupneic* P_{CO_2} *with the apnoea threshold suggested a further increase in the ventilatory sensitivity to hypocapnia in the 3rd compared with the 1st night (from 3.2 to 3.6* $L \cdot mmHg^{-1}$*). Correspondingly, the displacement of the eupneic* P_{CO_2} *to the left on the isometabolic line increased the overshoot in* V'_A *required to drive the* P_{CO_2} *to the apnoea threshold (from +21% to +32%). These changes were associated with a reduction in nocturnal periodic breathing in the 3rd compared with the 1st night at 4559 m. Reproduced and modified from Nussbaumer* et al. *2012 with permission.*

chemoreceptor sensitivity to hypoxia and hypercapnia, enhanced erythropoesis, and alterations in the endocrine system, metabolism and fluid balance. The reduced air density experienced at altitude lowers airflow resistance. Vital capacity is slightly reduced due to respiratory muscle weakness and pulmonary congestion. Oxygen uptake through the lungs is affected by a reduced alveolar–capillary oxygen gradient and a reduced transit time of blood through the pulmonary capillaries due to increased cardiac output. This causes diffusion limitation leading to hypoxaemia, especially during exercise.

Altitude-related illness

Table 1 summarises the different forms of acute altitude-related illnesses that occur within a few hours to 3–4 days after rapid ascent to altitudes of >2500 m. Acute mountain sickness (AMS) is the most common. It affects 10–40% of lowlanders rapidly ascending to 3000 m, and 40–60% of those ascending to 4500 m. Rapid ascent, high sleeping altitude, a lack of prior acclimatisation and individual susceptibility predispose to AMS. Symptoms start within 6–12 h of arrival at altitude and include headache, loss of appetite, nausea or vomiting, weakness, fatigue and insomnia. Diagnosis relies typical symptoms assessed using a standardised questionnaire, such as the Lake Louise score. If additional neurological signs such as ataxia, cognitive deficit and impaired vigilance develop, a potentially life-threatening high-altitude cerebral oedema (HACE) must be considered. Treatments of AMS include descent to lower altitude,

Table 1. Acute altitude-related illnesses

Condition	Main manifestations	Prevention	Treatment
AMS	Headache Loss of appetite Dizziness/light headedness Fatigue	Acclimatisation Slow ascent Acetazolamide 2 × 125–250 mg per day, starting 24 h before ascent or dexamethasone 2 × 4 mg per day 24 h before ascent	Non-steroidal analgesics Antiemetics Acetazolamide 2 × 250 mg per day More severe forms: descent; oxygen 2–6 $L \cdot min^{-1}$; dexamethasone (initially 8 mg *i.v.*, then 4 × 4 mg per day *p.o.*); acetazolamide (2 × 250 mg per day), eventually in combination with dexamethasone; portable hyperbaric chamber
HACE	Severe headache Ataxia Confusion Loss of consciousness	As for AMS	Immediate descent Oxygen (2–6 $L \cdot min^{-1}$), portable hyperbaric chamber Dexamethasone (initially 8 mg *i.v.*, then 4 × 4 mg per day *p.o.*) Check for accompanying HAPE Acetazolamide if descent delayed
HAPE	Cough Cyanosis Exercise intolerance Pulmonary hypertension	Acclimatisation Slow ascent Avoid overexertion Nifedipine 30–60 mg per day (extended-release formulation)	Immediate descent Oxygen 2–6 $L \cdot min^{-1}$ until oxygen saturation >90% or hyperbaric chamber Nifedipine 10–20 mg initially, switch to an extended-release formulation (nifedipine 30/60 mg) depending on blood pressure Treat accompanying AMS with dexamethasone

analgesics for headache, and acetazolamide. More severe forms of AMS and HACE require dexamethasone and oxygen, if available. Inflatable hyperbaric bags simulating descent to 1500–2500 m are also used. High-altitude pulmonary oedema (HAPE) is a noncardiogenic and noninflammatory oedema resulting from excessive elevation of pulmonary capillary pressure, uneven distribution of blood flow and impaired alveolar fluid clearance. HAPE is rare below 3500 m; it occurs in 2–4% of mountaineers within hours to 4 days of arrival at 4500 m. HAPE is promoted by rapid ascent, physical exertion and individual susceptibility. Manifestations of HAPE include excessive dyspnoea, dry cough, tachycardia, cyanosis, pulmonary crackles and low-grade fever. Chest radiography shows interstitial or alveolar opacities but a normal-sized heart. Descent, supplemental oxygen or both are nearly always successful in HAPE. Pulmonary vasodilators including calcium channel blockers (nifedipine) or phosphodiesterase inhibitors (sildenafil) may be administered to lower pulmonary artery pressure. If descent is impossible and oxygen is unavailable, a hyperbaric bag may be lifesaving. Table 1 provides a summary of methods of prevention and treatment for acute altitude-related diseases.

Chronic mountain sickness, an illness observed in long-term high-altitude residents, is characterised by severe hypoxaemia, excessive erythrocytosis and pulmonary hypertension. Those affected suffer from fatigue, dizziness, headache and confusion. Descent to a low altitude may provide relief. High-altitude pulmonary hypertension is another condition that affects long-term residents at altitudes of >2500 m. It causes dyspnoea, exercise intolerance and signs of right heart failure with oedema. It is associated with sleep apnoea but erythrocytosis is not a feature.

Patients with lung disease at altitude

Little is known about the risks of altitude exposure in patients with pre-existing lung disease. Recommendations are largely based on expert opinion.

In comparison with healthy individuals, patients with COPD suffer from more pronounced hypoxaemia at high altitude due to impaired pulmonary gas exchange. This results in dyspnoea, limited exercise performance and prominent periodic breathing with frequent central sleep apnoeas at altitude. In addition to their lung disease, patients have cardiovascular and other comorbidities that have to be taken into account when assessing their level of risk during mountain travel. Patients with severe COPD ($FEV_1 < 50\%$ predicted) and an S_{aO_2} of <92% at near sea level, should undergo specific individual assessment before travelling to altitude. A slow ascent rate, low sleeping altitude, continuation of regular bronchodilators and the use of supplemental oxygen should be considered. Further studies are required to determine whether preventive treatment with dexamethasone or acetazolamide is beneficial.

Reduced allergen burden can be expected at >1500 m. Conversely, inhalation of cold air may worsen asthma, especially in combination with exercise or hypoxia-induced hyperventilation. When travelling to altitude, asthma patients with controlled disease are advised to: take their usual medication; avoid strenuous exercise in a cold environment; and treat any exacerbation appropriately. Patients with uncontrolled, severe asthma should be cautioned against travelling to altitude.

Untreated OSAS patients residing near sea level and travelling to moderate altitude (>1600 m) experience an exacerbation of sleep apnoea with pronounced hypoxaemia and frequent central events. Sleep quality is worse at altitude and daytime testing shows impaired vigilance and elevated blood pressure. Combined treatment with CPAP and acetazolamide is advisable.

Pre-existing pulmonary hypertension may exacerbate during exposure to hypoxia at high altitude. This can result in dyspnoea and further impairment of exercise performance. Patients with more than mild pre-existing pulmonary hypertension should be counselled against high-altitude travel unless individual specific precautions are taken, such as oxygen therapy and adaptation of medication.

Table 2. Diving-related diseases

Affected organ	Type	Clinical manifestations
Barotrauma		
Face, ear, nose, teeth	Mask squeeze	Periorbital oedema and bleeding
	Sinus barotrauma	Pain, epistaxis, sinus haemorrhage, infraorbital paresthesia due to compression of the maxillary branch of the trigeminal nerve
	Tooth barotrauma	Pain, tooth fracture
	Middle ear barotrauma (tympanic membrane rupture)	Acute vertigo, pain
	Inner ear barotrauma (rupture of the round or oval window, perilymph fistula)	Vertigo, tinnitus, loss of hearing, nausea, vomiting
Lungs	Pneumothorax with or without tension	Acute dyspnoea, hypotension, loss of consciousness; associated arterial gas embolism (see below)
	Pneumomediastinum, pneumopericardium	Substernal pain exacerbated by swallowing or coughing
	Subcutaneous emphysema	Swelling, crepitus of the soft tissue of the neck and supraclavicular fossa, throat pain, hoarseness, dysphagia
Gastointestinal tract	Hollow viscous perforation	Abdominal pain, pneumoperiotoneum
Arterial gas embolism	Coronary gas embolism	Acute coronary syndrome
	Cerebral artery gas embolism	Loss of conciousness, confusion, visual disturbances, seizures, vertigo, headache, death
Decompression sickness		
Skin	Type I (mild)	Erythematous or purpuric skin rash (cutis marmorata)
Musculoskeletal system	Type I (mild)	Joint and/or muscle pain that can sometimes be relieved by bending (the bends); osteonecrosis can occur

(*Continued*)

Table 2. Continued

Affected organ	Type	Clinical manifestations
Audio-vestibular system	Type I (mild)	Dizziness, vertigo, nausea, vomiting, hearing loss
Respiratory system	Type I–II (mild to severe)	Cough, dyspnoea, chest pain
Whole body	Type I–II (mild to severe)	Headache, fatigue, generalised malaise
Nervous system	Type II (severe)	Brain and/or spinal cord injury (usually at levels below T11 and T12), altered consciousness, confusion, seizures, paresthesia, weakness or paralysis, urinary retention, bowel or bladder incontinence, sexual impotence

Diving-related diseases

Physiological consequences of underwater exposure

Immersion causes a central redistribution of the blood, which is increased by vasoconstriction due to cold water. This causes cardiac output and central venous pressure to increase, which enhances diuresis rendering the diver hypovolemic. Cold water exposure promotes heat loss and carries the risk of hypothermia. Lung volume reduces with increasing environmental pressure, in accordance with Boyle–Mariotte's law ($P_1 \times V_1 = P_2 \times V_2 = \text{constant}$). This results in a 50% reduction in lung volume by doubling of the intrathoracic pressure in an apnoea diver at 20 m below sea level. Nitrogen is fat soluble and with increased pressure more nitrogen is dissolved in the soft tissues at depth. On returning to the surface, the reduction in ambient pressure results in supersaturation of tissues with gases, which may cause bubble formation and, in some cases, adverse consequences (discussed further later). A self-contained underwater breathing apparatus (scuba) allows a diver to breathe air at ambient pressure from a pressurised bottle using a pressure regulator. Different diving gases are used (*e.g.* compressed air, nitrogen-oxygen, helium-oxygen or helium-nitrogen-oxygen mixtures) depending on depths and other criteria.

Diving-related illnesses

Barotrauma is the result of an air-containing body cavity's inability to equalise its pressure with the ambient pressure. Barotrauma of the lungs is the most serious form, and may result in arterial gas embolism causing circulatory disturbances, dysfunction of various organs due to ischaemia, and, if the central nervous system is affected, paresis and even loss of consciousness and death (table 2).

Decompression sickness, also referred to as caisson disease or the bends, occurs when inert gas in tissue becomes supersaturated during rapid ascent and decompression, and forms bubbles. These exert mechanical effects by distorting tissues, obstructing blood flow and initiating an inflammatory response. Most bubbles occur in the venous circulation and are filtered in the lungs preventing their passage into the systemic circulation. Exceptions include right-to-left intracardiac shunts (*e.g.* patent foramen ovale) or intrapulmonary shunts (*e.g.* arterio-venous malformations). To minimise the risk of decompression sickness, diving computers and tables assist in planning dive duration, with length depending on the depth, the ascent rate and decompression stops. Decompression sickness can be divided into mild forms that may be self-limiting (type I) and severe, life-threatening forms (type II). Various organs can be affected, as listed in table 2. Symptoms can occur immediately after surfacing but onset can also be delayed for up to 48 hours. Essential emergency treatment includes: immediate on-site administration of 100% oxygen; fluid resuscitation to replace the intravascular volume depletion; and timely hyperbaric oxygen therapy for 5–6 h according to standard protocols.

Immersion pulmonary oedema is a rare condition that occurs in otherwise healthy swimmers and divers, particularly in cold water. Manifestations include dyspnoea, cough and frothy sputum, which may lead to a critical condition depending on the circumstances. Clinical evaluation is likely to reveal pulmonary rales, hypoxaemia and infiltrates on the chest radiograph. The pathophysiology of the disease is not clear, and symptoms resolve spontaneously within hours to a few days.

Diving with lung disease

Virtually all diseases affecting the lung parenchyma and/or airways are associated with an uneven distribution of ventilation due to differences in time constants between the lung regions. This predisposes to barotrauma and has potentially serious complications. Diving with a lung disease such as COPD or interstitial lung disease (ILD) is therefore generally discouraged. Recommendations based on expert opinion suggest that patients with asthma should not dive unless their disease is well-controlled and spirometry is normal.

Further reading

- Bärtsch P, *et al*. (2013). Acute high-altitude illnesses. *N Engl J Med*; 368: 2294–2302.
- Bloch KE, *et al*. (2015). Patients with obstructive sleep apnea at altitude. *High Alt Med Biol*; 16: 110–116.
- Bloch KE, *et al*. (2015). Sleep at high altitude: guesses and facts. *J Appl Physiol*; 119: 1466–1480.
- Bove AA (2014). Diving medicine. *Am J Respir Crit Care Med*; 189: 1479–1486.
- Coop CA, *et al*. (2016). SCUBA diving and asthma: clinical recommendations and safety. *Clinical Rev Allerg Immunol*; 50: 18–22.
- Furian M, *et al*. (2018). Exercise performance of lowlanders with COPD at 2590 m: data from a randomized trial. *Respiration*; 95: 422–432.
- Furian M, *et al*. (2018). Efficacy of dexamethasone in preventing acute mountain sickness in COPD patients: randomized trial. *Chest*; 154: 788–797.
- Furian M, *et al*. (2019). Effect of dexamethasone on nocturnal oxygenation in lowlanders with chronic obstructive pulmonary disease traveling to 3100 meters: a randomized clinical trial. *JAMA Netw Open*; 2: e190067.
- Latshang TD, *et al*. (2012). Effect of acetazolamide and autoCPAP therapy on breathing disturbances among patients with obstructive sleep apnea syndrome who travel to altitude. A randomized controlled trial. *JAMA*; 308: 2390–2398.

- Levett DZH, *et al*. (2008). Bubble trouble: a review of diving physiology and disease. *Postgrad Med J*; 84: 571–578.
- Nussbaumer-Ochsner Y, *et al*. (2007). Lessons from high-altitude physiology. *Breathe*; 4: 123–132.
- Nussbaumer-Ochsner Y, *et al*. (2010). Air travel and altitude. *In*: Ayres JG, *et al*. 2010. ed. Environmental medicine. London, Hodder Arnold.
- Nussbaumer-Ochsner Y, *et al*. (2012). Sleep and breathing in high altitude pulmonary edema susceptible subjects at 4,559 meters. *Sleep*; 35: 1413–1421.

Index

A

AAT (α_1-antitrypsin) deficiency *see* α_1-antitrypsin deficiency (AATD)
abacavir, hypersensitivity 690
abatacept 408
ABCA3, gene mutations 589
abscess
  lung *see* lung abscess
  peritonsillar/periodontal 672, 673
acclimatisation mechanisms 779–780
ACE2/Ang(1-7)/Mas receptor pathway 216
ACE inhibitors *see* angiotensin-converting enzyme (ACE) inhibitors
acetazolamide 532
N-acetylcysteine 114
  COPD exacerbation prevention 337
  idiopathic interstitial pneumonias 576
  idiopathic pulmonary fibrosis 556
achalasia 702
acid–base disorders 29
  arterial blood gas analysis 60
  causes 63, 64–65, 66
  diagnosis 63, 64
  pH, P_{aCO_2}, bicarbonate levels 63, 64
acid-fast bacilli (AFB) 201, 202, 417, 430
  in bronchiectasis 355
acid-fast stains 7, 8, 11, 202
acid maltase deficiency 654, 656
Acinetobacter baumannii 384
acinus 3
  development 6
acquired immune response 21–25
acquired immunodeficiency 390, 400, 404–409
acrylate cement, embolism 603
Actinomyces, staining method 11
acute bronchitis 320–321
acute eosinophilic pneumonia 616–617
  drug-induced 606
acute exacerbations of COPD (AECOPD) 543
  acute respiratory failure 295–296, 543–544
  hypercapnia persisting after 550
  hypercapnic respiratory failure 543–544
  management 544
    noninvasive ventilation 544, 546, 547, 549
    noninvasive ventilation withdrawal 550
  see also chronic obstructive pulmonary disease (COPD) exacerbations
acute hypoxaemic respiratory failure (AHRF) 549–550
acute interstitial pneumonia (AIP) 297
acute lung injury (ALI) 299
  aspiration of gastric acid 411, 413
  direct and indirect, causes 300
  drug-induced 598
  primary graft dysfunction 290–291
  radiation-induced 612–613
  see also acute respiratory distress syndrome (ARDS)
acute lysis pneumopathy 711
acute mountain sickness (AMS) 534, 780, 781
acute myeloid leukaemia 16
acute nitrofurantoin lung 599
acute-on-chronic respiratory failure 297, 541
  causes 543–544
    infections 266, 543
  diagnostic features 294
  pathophysiology 543–544
acute-on-chronic ventilatory failure 266
acute phase proteins, in COPD 340, 341
acute promyelocytic leukaemia 17, 710, 712
acute respiratory distress syndrome (ARDS) 11, 299–303
  arterial blood gas analysis 62–63, 299
  aspiration of gastric acid and 413
  Berlin definition/criteria 299
  categories, hypoxaemia levels 63, 299
  causes (direct/indirect lung injury) 300
  chest radiograph 300
  drug-induced 599, 607
  exudative phase (acute) 300, 301
  fibroproliferative phase 300, 301
  hyperinflammatory type 300
  incidence 299
  mild, moderate and severe, criteria 63, 299
  in miliary TB 435
  pathophysiology 300, 301
  treatment 300, 302
acute respiratory failure (ARF) 293–298, 541
  causes 294, 542
  clinical features 293
  clinical settings 294, 295–298
    acute infiltrative pneumonia 294, 296, 297
    chronic infiltrative disease exacerbation 297
    community-acquired pneumonia 294, 296–297
    COPD and asthma exacerbations 295–296, 543
    diffuse alveolar haemorrhage 294, 296, 297
    neuromuscular diseases 294, 296, 298, 653
    pulmonary embolism 294, 296, 298
    severe haemoptysis 294, 296, 297–298
    tension pneumothorax 294, 296, 298
    upper airway angio-oedema 294, 295, 296
    wheezing *vs* lung congestion 297
  diagnostic approach 294, 295
  hypoxaemic, causes 542
  management 293, 295–298
    NIV *see* noninvasive ventilation (NIV)
  pathophysiology 294
  type 1 (hypoxaemic) 293, 542
  type 2 (hypercapnic) 293, 294, 543
acute upper airway obstruction 294, 295, 296
acute vasoreactivity testing 634
ACVLR1 gene mutations 646
adaptive servoventilation (ASV) 267, 532, 533
adenocarcinoma, lung
  cytology 14

    molecular genetic abnormalities 455, 448, 449–450
    screening and 455
    see also lung cancer
adenoid cystic carcinoma
    cytology 16
    tracheal obstruction 133
adenosine
    bronchial provocation test 81, 82
    in exhaled breath condensate 191
adenosine challenge test 81, 82
adenosine deaminase 510, 664
adenosine triphosphate (ATP), in exhaled breath condensate 191
adenotonsillectomy 527
adenovirus infections, cytological changes 11
adipose tissue 719
ADJUST-PE study 621, 623
adjuvant chemotherapy 464
    see also chemotherapy
adolescents
    asthma management 316
    smoking 258
adrenaline, plasma, increase in COPD 219
adrenocorticotropic hormone (ACTH), ectopic secretion 491, 493
adult pulmonary Langerhans cell histiocytosis *see* Langerhans cell histiocytosis (LCH)
advance care planning 249–250, 251, 579
advanced glycation end-products (AGEs) 221
adverse drug reactions 596, 597
    see also drug-induced respiratory disease (DIRD); specific drugs
AECOPD *see* acute exacerbations of COPD (AECOPD)
aetiological fraction 764
afatinib 465, 466
    lung cancer 465, 466
agammaglobulinaemia 401
age
    lung cancer diagnosis 461
    lung transplantation and 289
    pulmonary tuberculosis risk 418
air
    manual aspiration, spontaneous pneumothorax 668–669
    quality, importance 771
air-conditioner lung 560
'air crescent' sign 391
airflow limitation
    asthma 310–311, 312
        COPD *vs* 314–315
    COPD, cardiac events and 694
    see also airflow obstruction
airflow measurement 49–51
airflow obstruction
    asthma 308, 309, 310, 314
    COPD 309, 314, 325, 327
    COPD exacerbation 334
    heart failure 695
    see also airflow limitation; airway obstruction
air hunger 100, 104
air pollution 771–778
    asthma and 774
    biological mechanisms 777
    children and 771
    chronic bronchitis and 321
    COPD and 324, 772
    indoor 775–776
        pollutants 775
    lung cancer risk 454, 773, 776
    outdoor 771, 772–775
    reduction, clean air principles 772
    short-term and long-term effects 771, 772
    sources 771
    traffic-related 771, 772, 774
airspace de-recruitment 542
airway(s)
    anatomy 3–4
    arterial supply 3
    central lesions, biopsy and sampling techniques 208
    cilia *see* cilia
    conductance 49
    drug-induced compromise 596, 597, 608–609
    epithelial injury
        by aspiration of gastric fluids 411
        idiopathic pulmonary fibrosis and 554
    infections *see* respiratory infections
    inflammation *see* airway inflammation
    reflux, chronic cough 111, 112, 113
    residual volume affected by 85
    smooth muscle, relaxation, β_2-agonists 345
    stenosis 133, 370
    stenting 130, 133, 134
    T-cell types in smokers 21
    upper *see* upper airway
    venous drainage 3
    see also bronchi; bronchioles; trachea
airway clearance techniques 233, 234, 235
    bronchiectasis 235, 355–356
    classification 237
    COPD 234
    cystic fibrosis 235
    in mucus hypersecretion 115
    neuromuscular disorders 236–237, 658
    primary ciliary dyskinesia 742
airway diseases
    asthma *see* asthma
    bronchiectasis *see* bronchiectasis
    bronchitis *see* bronchitis
    congenital *see* congenital airway disease (CAD)
    in connective tissue diseases 724, 725
    COPD *see* chronic obstructive pulmonary disease (COPD)
    drug-induced 599
    hypercapnic respiratory failure due to 543
    infections *see* respiratory infections
    nodular 360

  occupational 752
  rare 358–363
    classification 359
    clinical features 359
    focal and diffuse types 359
  upper airway *see* upper airway disease
airway hyperresponsiveness (AHR)
  asthma 312–313
  bronchial provocation testing 77, 79, 80, 82
airway infections *see* respiratory infections
airway inflammation
  assessment in asthma 314
  bronchitis 320
  chronic 322
    asthma 308, 322
    asthma *vs* COPD 314–315
    chronic bronchitis 321
    COPD 20–21, 322, 325, 339, 340, 341
    see also chronic obstructive pulmonary disease (COPD)
  eosinophilic 188
    asthma 188, 189
    chronic cough 188
    markers of 190
    nonasthmatic eosinophilic bronchitis 615
  large airway, chronic bronchitis 325
  mucus composition 114
  neutrophilic, COPD 188
  omalizumab reducing 350
  pH of exhaled breath condensate 190
  small airway, COPD 325
  sputum analysis 188
airway obstruction
  asymptomatic/mild, exertional dyspnoea 105
  benign central, management 133
  central, interventional pulmonology for 132–133
  proximal, interventional procedures 133
  see also airflow obstruction
airway resistance (R_{aw}) 30–31, 32, 48–49
  definition 48–49
  measurement 49–51
alectinib 449–450
alemtuzumab 408
ALICE study 695
A-lines 162, 163
aliskiren 217
ALK gene rearrangement, lung cancer 449–450, 467
alkylating agents, pulmonary toxicity 598
allergen(s) 304
  allergic rhinoconjunctivitis 225
  avoidance 223, 224
  hypersensitivity pneumonitis 559, 560
allergen bronchial provocation test 80, 82
allergen challenge tests 80, 82, 313
allergen desensitisation *see* allergen immunotherapy (AIT)
allergen immunotherapy (AIT) 223–226
  in allergic rhinoconjunctivitis 224–225, 305
  in asthma 225
  contraindications 226
  delivery route 224
  indications 223–224
  insect venom 224
  principle/concept 224
  side-effects 225–226
allergic alveolitis *see* hypersensitivity pneumonitis (HP)
allergic bronchopulmonary aspergillosis (ABPA) 12, 616
  in cystic fibrosis 733
  testing 355
allergic diseases 223
allergic reactions
  air pollution role 774
  seasonal or perennial 223
  to venom 224
allergic rhinitis/rhinoconjunctivitis (ARC) 224–225, 304–305, 374
  clinical features and diagnosis 305
  definition 374
  differential diagnosis 305, 374
  epidemiology 304–305
  management 224–225, 305
  polyallergic or monoallergic 225
allergy tests 80, 82
  asthma 313
alpelisib 451
altitude, high *see* high altitude; high altitude-related disease
alveolar–arterial oxygen tension gradient ($P_{A\text{-}aO_2}$) *see under* oxygen
alveolar–capillary exchange 54
alveolar–capillary membrane, diffusion across 35, 36
alveolar cells, hyperplasia 11
alveolar ducts 3
alveolar epithelium
  injury, idiopathic interstitial pneumonias 569, 574, 579
  reactive changes 10
alveolar filling syndromes, BAL fluid findings 141, 143
alveolar haemorrhage
  diffuse *see* diffuse alveolar haemorrhage (DAH)
  drug-induced 599
  haemoptysis due to 115
alveolar hypoventilation 34–35
  acute-on-chronic respiratory failure 294
  causes 542
  type 2 respiratory failure 294, 542
  see also hypoventilation syndromes
alveolar macrophages (AMs) 13
  in BAL fluid 140, 141
  in COPD 24
  in hypersensitivity pneumonitis 558
  in pulmonary alveolar proteinosis 589, 590
  smokers, BAL fluid 141
  surfactant in 589

- alveolar opacities, perihilar, drug-induced respiratory disease 601
- alveolar pneumonia, chest radiography 295
- alveolar pressure (P_{alv}) 30, 31, 32, 48
  - body plethysmography and 49–50
  - measurement 51
- alveolar proteinosis
  - acute silicosis causing 750–751
  - cytological changes 13
  - *see also* pulmonary alveolar proteinosis (PAP)
- alveolar shunt 38
- alveolar ventilation (V'_{A}) 28, 29
  - reduced
    - high altitude 780
    - hypercapnic respiratory failure 542, 543
    - sleep-related hypoventilation 536
- alveolar volume (V_{A})
  - measurement 55, 56
  - physiological influences 57
  - reduced
    - causes 57
    - effect on T_{LCO} and K_{CO} 57
  - T_{LCO} calculation and 55–56, 57
- alveoli
  - anatomy 3
  - carbon monoxide uptake 54, 55, 56, 58
  - development 6
  - diameter, oxygen diffusion 35
  - measurements, T_{LCO} *see* transfer factor of the lung for carbon monoxide (T_{LCO})
- amantadine, influenza treatment 395
- AMBITION trial 634
- ambrisentan 577, 634
- ambulatory oxygen therapy 254
- American Academy of Sleep Medicine (AASM) 522–523, 530
- American Society of Anesthesiologists (ASA) 91
- American Thoracic Society (ATS)
  - chest radiography indications 155, 156
  - community-acquired pneumonia, criteria 380
  - connective tissue diseases 723
  - COPD exacerbations 332
  - dyspnoea 100
  - idiopathic interstitial pneumonia 568, 570, 574
  - idiopathic pulmonary fibrosis 554
  - malignant pleural effusions 510
  - noninvasive ventilation (NIV) 546
  - nontuberculous mycobacterial disease 444
  - pulmonary rehabilitation 239
  - sarcoidosis 564
  - TB testing 204
  - T_{LCO} and T_{LNO} 58
- amikacin therapy, NTM infections 445
- aminophylline 347
- amiodarone 698–699
  - pharmacokinetics and metabolism 598, 698
  - pulmonary toxicity (APT) 598, 603, 606–607, 698–699
    - clinical features 699
    - incidence 699
    - lung disease risk 699
    - mechanism 698, 699
    - pulmonary follow-up 699
    - treatment 699
- amiodaronoma 606
- ammonium ions 67
- amoxicillin–clavulanate therapy
  - chronic rhinosinusitis 307
  - COPD exacerbations 335
  - pulmonary tuberculosis 424
- amphiphilic granules 13
- amphotericin B 391, 407
- amylase, in pleural fluid 663
- amyloid A amyloidosis 592
- amyloid light chain (AL) amyloidosis 360, 593
  - respiratory symptoms 593
- amyloidosis 360, 592–594
  - clinical presentation 592
  - laryngeal 593
  - localised to respiratory tract 593
  - parenchymal pulmonary 593
  - primary tracheobronchial 360
  - systemic, complicating respiratory diseases 592–594
  - tracheobronchial 593
- amyotrophic lateral sclerosis (ALS)
  - long-term ventilation 268, 269
  - respiratory muscle weakness 653–654
  - sleep-related hypoventilation syndromes 538
- anaemia, chemotherapy-induced 465
- anaerobes
  - aspiration pneumonia 412
  - lung abscess 279
  - pleural infections 277
- anaesthetic complications 277, 743
- analgesia, palliative care 250
- anaphylaxis
  - ACE inhibitors and 216
  - drug-induced 598
- anaplastic lymphoma kinase (ALK) 449–450
- anatomic resection
  - in lung cancer 475
  - *see also* lobectomy; pneumonectomy
- anatomy, respiratory system 1–6
  - diaphragm 5–6
  - hila, pulmonary 4
  - lungs 2–5
  - mediastinum 5, 514
  - trachea and bronchi 3–4, 358
- ANCA *see* anti-neutrophil cytoplasmic antibodies (ANCAs)
- aneurysmal sacs 647
- angina, COPD with 692
- angiography, CT *see* computed tomography (CT) angiography (CTA)
- angiomyolipoma (AML) 586, 588
- angio-oedema
  - drug-induced 596, 598, 608–609

    - management 609
  - upper airway, bradykinin-mediated 295, 296
- angioplastic lobectomy 477
- angiotensin-converting enzyme (ACE) 217
- angiotensin-converting enzyme (ACE)2/Ang(1-7)/ Mas receptor pathway 216
- angiotensin-converting enzyme (ACE) inhibitors
  - adverse effects 598, 604
  - angio-oedema due to 598, 608–609
  - cough due to 216, 609
  - cough sensitivity 111
  - idiopathic interstitial pneumonias 576
  - impact on lung 216, 598
- angiotensin II 216, 217
- angiotensin II type 1 (AT1) receptor 216
  - blockers 216
- anion gap (AG) 68
- anorexigen drugs 628–629
- ANOVA 769
- anti-angiogenic drugs, lung cancer 467
- antiarrhythmic drugs, effects on lungs 698–699
- antibiotics
  - acute bronchitis 321
  - aspiration pneumonia 412
  - bronchiectasis treatment 356
  - chronic rhinosinusitis 307
  - community-acquired pneumonia 380, 381
  - COPD exacerbations 329, 330, 335
  - cystic fibrosis 731, 732
  - first-line, COPD exacerbations 335
  - hospital-acquired pneumonia 385, 386–387
  - inhaled, in bronchiectasis 356
  - lung abscess 280
  - macrolide *see* macrolide antibiotics
  - for MDR pathogens 386, 387
  - for pleural infections 275, 276, 277
  - pneumonia 380
  - primary ciliary dyskinesia 743
  - prophylactic
    - bronchiectasis 356
    - cystic fibrosis 731
    - primary ciliary dyskinesia 743
    - pulmonary vasculitis 644
  - pulmonary infections in primary immunodeficiency 678–679
  - pulmonary vasculitis 644
  - purulent sputum management 114
  - resistance
    - community-acquired pneumonia 379
    - macrolides 379
  - upper respiratory tract infections 375
  - ventilator-associated pneumonia 385, 386–387
  - antibodies
  - in COPD 22
  - deficiency, primary 675, 676
  - monoclonal *see* monoclonal antibodies; specific drugs
- antibody tests, for respiratory infections 197–198
- anti-CD1a antibodies 582
- anti-CD207 (langerin) antibodies 582
- anticholinergic therapy 346–347
  - asthma 346
  - COPD 346
  - mode of action 346
  - nebulised 346
  - side-effects 346–347
- anticoagulants, idiopathic interstitial pneumonias 577
- antifibrotic drugs 576
  - IFN-γ 575–576
- antifungal drugs, *Aspergillus pneumonia* 391
- antigenic drift 393
- antigen-presenting cells (APCs) 24, 581
- anti-glomerular basement membrane (anti-GBM) disease 297
- anti-IgE 350
- anti-IL-5 antibodies 350
- anti-inflammatory therapy
  - idiopathic interstitial pneumonias 574–575
  - statins role, in asthma and COPD 217, 218
  - sulfonylureas action 220
  - *see also* corticosteroid therapy; nonsteroidal anti-inflammatory drugs (NSAIDs)
- antileukotrienes 349–350
  - clinical use 349–350
  - mode of action 349
  - side-effects 350
- anti-neutrophil cytoplasmic antibodies (ANCAs) 637
  - cytoplasmic 637, 640
  - diffuse alveolar haemorrhage and 297, 608
  - drug-induced respiratory disease 596, 604, 605
  - eosinophilic granulomatosis with polyangiitis 640, 642
  - perinuclear 637, 640
  - primed neutrophils interacting 637–638
  - subcategories 637
  - vasculitides with 297, 637
- antioxidants, idiopathic interstitial pneumonias 576
- anti-PDL1 drugs *see* PD-L1, antibodies/inhibitors
- anti-platelet drugs, in COPD 342
- antiretroviral therapy (ART) 681, 682, 683, 686
  - beneficial impact 689
  - immune reconstitution disease (IRD) 443, 687, 689–690
  - respiratory symptoms due to 689–690
  - TB and HIV co-infection 443, 687, 689–690
- α_1-antitrypsin (AAT) 744, 745
  - circulating levels 745
  - in hepatocytes 745
  - infusions 746
- α_1-antitrypsin deficiency (AATD) 324, 355, 744–747
  - clinical features 745
  - COPD in 745, 746
  - diagnosis 745–746
  - emphysema 744, 745
  - genetic variants 744, 745
  - homozygous 324–325
  - inheritance 744, 745, 746

  - MS heterozygotes 745
  - null variants 744, 745
  - pathophysiology 744
  - PiZZ (proteinase inhibitor homozygous) 744
  - SZ heterozygotes 745
  - treatment 746
- anti-tuberculosis drugs
  - extrapulmonary tuberculosis 434
  - for MDR-TB 424, 425
  - nontuberculous mycobacterial infections 445
  - pulmonary tuberculosis 421–424
    - first-line drugs 204, 205, 422
    - oral reserve drugs 423–424
    - second-line drugs 204, 423
  - resistance
    - detection 204–205
    - molecular detection 205–206
- antitussive agents, chronic cough management 112
- anxiety 241
- apnoea
  - central *see* central sleep apnoea (CSA)
  - obstructive *see* obstructive sleep apnoea–hypopnoea syndrome (OSAHS)
- apnoea–hypopnoea index (AHI) 523
- ARDS *see* acute respiratory distress syndrome (ARDS)
- ART (Alveolar Recruitment for ARDS Trial) 302
- arterial blood gas (ABG) analysis 60–69
  - abnormal, causes 61
  - acid–base disorders 60
  - acute respiratory failure 294
  - asthma 313
  - evaluation 61–63
    - equipment for 60
  - hepatopulmonary syndrome 705
  - interpretation 60–61, 67, 68
  - pneumonia 379
  - respiratory failure 541
  - sleep-related hypoventilation syndromes 536
- arterial embolisation, pulmonary arteriovenous malformations 648
- arterial gas embolism 783
- arterial hypoxaemia *see* hypoxaemia
- arterial oxygen desaturation *see* oxygen
- arterial pH *see* pH, arterial
- arteriovenous malformations, pulmonary *see* pulmonary arteriovenous malformations (PAVMs)
- arthritis
  - rheumatoid *see* rheumatoid arthritis (RA)
  - tuberculous 436
- 5As approach, smoking cessation 263, 264
- asbestos 506
  - exposure 140
  - lung cancer 752
- asbestos bodies 140
- asbestosis 750, 751
- asbestos-related pleural diseases 752
  - *see also* malignant pleural mesothelioma (MPM)
- ASCEND trial 576
- aspergillosis
  - allergic bronchopulmonary 12, 616
    - in cystic fibrosis 733
  - invasive, diagnostic criteria 391
- *Aspergillus* infection, evidence/detection 407
- *Aspergillus* pneumonia (AP) 391, 405, 407
  - in neutropenia 405
  - post-transplant 407
- aspiration 411
  - detection 412–413
  - of gastric fluids 411, 701
    - airway/lung damage 411–412, 413
    - microaspiration 411, 578
  - infectious 412
  - large volume acute 411, 412
  - low volume chronic 411, 412
  - pulmonary conditions due to 413–414
  - symptoms 412–413
  - therapeutic approaches 413
  - *see also* gastro-oesophageal reflux disease (GORD)
- aspiration-induced lung injury 413
- aspiration pneumonia 296, 377–378, 412
  - causative agents 412
  - in connective tissue diseases 724, 725
- aspiration pneumonitis 411–415
- aspirin sensitivity 306, 349
- asplenia, opportunistic infections 409
- assessment, physical *see* physical examination
- assessment, pre-operative *see* pre-operative assessment
- asthma 308–319
  - airflow obstruction 308, 309, 310
  - allergic, allergen immunotherapy 225
  - altitude effects 782
  - aspirin-sensitive 349
  - atopic, exhaled nitric oxide fraction (*F*ENO) 314
  - 'atypical,' in cystic fibrosis 730
  - chronic airway inflammation 308, 322
  - clinical features 308, 309–310, 314
    - cough 111
    - dyspnoea 104, 309
    - GINA assessment of control 317
    - wheezing 297, 310
  - cold air inhalation 782
  - comorbidities 215, 315, 318
    - COPD 315, 333
    - GORD 414
    - heart disease 693
  - COPD *vs* 308, 309, 312, 313
    - ancillary tests 315
    - symptoms and pulmonary function tests 314–315
  - definition 308, 717
  - diagnosis
    - airway hyperresponsiveness 312–313
    - airway inflammation assessment 314
    - allergy tests 313
    - ancillary tests 315
    - arterial blood gas analysis 313

    biomarkers in exhaled breath condensate 191, 192
    biomarkers in sputum 189
    bronchial provocation testing 77, 79, 80, 82, 312–313
    exhaled breath analysis 191, 192
    FEV$_1$ and vital capacity 312
    flow-chart 311
    imaging 313
    induced sputum and *F*ENO 314
    lung function tests 312
    minimum requirements 309–313
    peak expiratory flow (PEF) 311, 312
    physical examination 310–311
    reversibility testing 312
  differential diagnosis 310, 312, 313, 374
    COPD *vs* 308, 309, 312, 313, 314–315
  diving and 785
  drug-induced 598, 609
  dyspnoea, predictors 104
  early-onset obese 718
  environmental tobacco smoke exposure 775, 776
  eosinophilic inflammation leading to 615
  exacerbations 310, 318
    air pollution 772, 775
    management 348
    severe *see below*
    smoking and 259
  exercise-induced 310
  exertional dyspnoea 104
  family history 308, 309, 313
  genetics 309, 774
  heterogeneous disease 308–309
  high altitude 782
  histology 309
  inflammatory phenotypes 322
  late-onset
    in eosinophilic granulomatosis with polyangiitis 638
    nonatopic, in obesity 718
  management/treatment 316–318
    anticholinergic therapy 346
    anti-IgE (omalizumab) 350
    anti-IL-5 350
    antileukotrienes 349
    β_2-adrenergic agonists 317, 344–345
    biologics 317
    bronchoscopic 131
    controller medications 317, 344
    corticosteroids 348–349
    of exacerbations 318
    immunosuppressive drugs 351
    immunotherapy 318
    inhaled corticosteroids 308, 345, 348
    initial 317
    long-acting β_2-agonists and corticosteroids 345
    monitoring 317
    pharmacological 317, 344–352
    pharmacological (long-term) 316–318
    reliever medications 317, 344, 345
    respiratory physiotherapy 234
    stepwise approach 316
    theophylline 347
  medical history 309–310
  mild 310
  mild exacerbations 318
  in obesity 717–718
    management 721
  occupational *see* occupational asthma
  ‘phenotypes’ 308–309, 322
    neutrophilic 322
  poorly controlled, cystic fibrosis 730
  in primary immunodeficiency 676
  risk factors 308, 757
    air pollution 774
    building dampness and mould 776
  severe 315
    obesity and 718
  severe exacerbation 313
    acute respiratory failure 295–296
    clinical features 311
    management 318
  severity, assessment 309, 316
  smoking relationship 259, 315, 317
  sputum eosinophilia 188, 189
  systemic pharmacotherapy impact 215–216
    ACE inhibitors and AT1R blockers cautions 216
    β-blockers 219–220
    hypoglycaemic drugs 220
    statins 217–218
  total lung capacity 84
  triggers 310
  well-controlled, operative risk and 92
  wheezing and 297, 310
  work-exacerbated 748, 749
  work-related *see* work-related asthma (WRA)
asthma–COPD overlap (ACO)
  exacerbations 333
  treatment 346
  see also asthma; chronic obstructive pulmonary disease (COPD)
AT1R blockers 216
ataxia-telangiectasia 401
atelectasis
  after endoscopic lung volume reduction 283, 284
  ARDS pathophysiology 300, 301
  chest radiography 295
  in cystic fibrosis 734
  in primary ciliary dyskinesia 743
atezolizumab 227, 228, 467
  NSCLC 467, 468
  SCLC 468
atmospheric pressure (P_{atm}) 30, 31, 49, 779
atovaquone, in *Pneumocystis* pneumonia 684, 685
atrial fibrillation 330, 531, 597, 693
  catheter ablation, respiratory disease after 603, 610

atropine 346
attributable risk (AR) 763, 764
attributable risk percentage 764
auramine O/auramine–rhodamine dyes 201
auscultation 123
autofluorescence 128
autoimmune diseases, connective tissue, affecting lung 722
autoimmune thrombocytopenia 709
autonomic nervous plexus, mediastinum 5
avelumab 230
avian influenza viruses 397
azathioprine therapy 575
    idiopathic pulmonary fibrosis 556, 575
    pulmonary vasculitis 643
azithromycin 115
    after lung transplantation 291
    in bronchiectasis 357
    COPD exacerbation management 115
    COPD exacerbation prevention 337
    in *Pneumocystis* pneumonia 685
    in primary ciliary dyskinesia 743

B

bacteraemia, in HIV infection 683
bacterial infections
    acute bronchitis 320
    aspiration pneumonia 412
    community-acquired pneumonia 274, 275, 296, 379
    complications, in HIV infection 683
    COPD exacerbation 333, 334
    COPD pathogenesis 22, 23, 25
    cystic fibrosis 731, 732
    diagnosis *see* microbiological testing
    hospital-acquired pneumonia 384–385
    immunocompromised hosts 389
        HIV-infected patients 682–683
        primary immunodeficiency 675, 676
    lung abscess 279–280
    pleural infections 274, 275, 277
    see also respiratory infections; specific infections
bagassosis 560
BAL *see* bronchoalveolar lavage (BAL)
balloon pulmonary angioplasty 636
BALT (bronchial-associated lymphoid tissue) lymphoma 678, 724
bariatric surgery 538, 720
barium swallow 413
barometric pressure 779
barotrauma 784
    pulmonary 783, 784, 785
B-cell(s) (B-lymphocytes)
    activation 22
    in COPD 21, 22
    deficiency, incidence, gene and infections 401, 404
    IgM^+, in COPD lymphoid follicles 22
    memory 22
    oligoclonal, in COPD 22
    types in lung 22
B-cell activating factor (BAFF) 21, 22
B-cell lymphomas 16, 688
bedside digital radiography 158
bedside radiography 157
behavioural modification/support
    obesity management 720
    smoking cessation 262, 263
behaviour change, enhanced physical activity and 241
bends, the (decompression sickness) 783–784, 784–785
benign non-neoplastic disorders, cytology 12–14
benralizumab 350
bereavement 252
Bernoulli’s law 86
β_2-adrenergic agonists 219, 344–346
    in asthma 317, 344–345
    in COPD 329, 344–345
    long-acting *see* long-acting β_2-agonists (LABA)
    mode of action 344–345
    safety 345–346
    short-acting *see* short-acting β_2-agonists (SABA)
    side-effects 345
    tolerance 346
β_2-adrenoreceptors (β_2-ARs) 218–219, 344–345, 698
    inverse agonists 219
β-blockers 218–220
    β_1-AR selective 220, 698
    in cardiac disease, effects on lungs 698
    cardioselective, effect on lungs 698
    contraindicated in asthma 698
    in COPD 342, 698
    underuse, in concomitant lung disease 698
    upregulation of β_2-ARs, in COPD 218–219
bevacizumab therapy 467
    malignant mesothelioma 470
    nonsmall cell lung cancer 467
    pleural tumours 512
    side-effects 467
bias 766–767
    types 766
bicarbonate 29, 63
    in acid–base disorders 63, 64
biliary tract disease, in cystic fibrosis 736
bioactivation of drugs 598
biomarkers
    drug-induced respiratory disease 605
    in exhaled breath 190, 191, 192
    in sputum 188, 189
    tobacco smoke exposure 264
biomass fuels, indoor air pollution 775–776
biopsy 207–209
    bronchial 127
    central endobronchial lesions 128, 207–208
    forceps 207

  lesions in hilar-mediastinal region 209
  lung *see* lung biopsy
  lung cancer 456
  peripheral lesions 208–209
  pleural, closed percutaneous needle 510
  pleural effusion cause 662
  pulmonary vasculitis 639
bird fancier's lung 557, 558, 560, 561
blebs, spontaneous pneumothorax 667
bleeding, alveolar *see* alveolar haemorrhage
bleomycin pulmonary toxicity 598
B-lines, transthoracic ultrasound 162, 163, 166
blood culture 194, 196
blood gas analysis *see* arterial blood gas (ABG) analysis
blood supply
  bronchial 115
  diaphragm 6
  lungs 4–5
  mediastinum 5
  pleura 1
  thymus 5
  trachea 3
blood urea, pneumonia 379
'blue bloaters' 325
'blue spells' 368
BMPR2 gene mutation 629
body composition, in COPD 245
body mass index (BMI)
  asthma relationship 718
  obesity 716, 717, 719
body plethysmography 49–51, 87, 88
Bohr technique 38
bone(s)
  in cystic fibrosis 737
  metastases 498–499
  tuberculosis 436
bone marrow transplantation
  opportunistic infections 405
  see also haematopoietic stem cell transplantation (HSCT)
bone scintigraphy
  bone metastases 498–499
  chest pain investigation 109
Bordetella parapertussis 373
Bordetella pertussis 373
  acute bronchitis 320, 321
Borg scale 99–100
Bornholm disease 109
bosentan
  idiopathic interstitial pneumonias 576–577
  pulmonary arterial hypertension 634
Boyle's law (Boyle–Mariotte's law) 88, 784
brachytherapy 131, 482
  lung cancer 470, 482
bradykinin 216, 217, 295, 598
BRAF gene mutations
  lung cancer 449
  pulmonary Langerhans cell histiocytosis 581–582
  V600E 449, 581–582
BRAF inhibitors, adult pulmonary Langerhans cell histiocytosis 584
breast cancer, metastasis 495, 496, 498, 507
breath, stacked 237
breath-actuated pressurised metered-dose inhalers (BA-pMDI) 212, 213
breath-holding, T_{LCO} measurement 54–55
breathing
  control, nasal CPAP and 526
  difficulties *see* dyspnoea
  disturbances, sleep-related *see* central sleep apnoea (CSA); obstructive sleep apnoea (OSA)
  dysfunctional, respiratory physiotherapy 234
  expiration *see* expiration
  inspiration *see* inspiration
  inspiratory work 31–32
  mechanics *see* respiratory mechanics
  unstable, in obstructive sleep apnoea 523, 526
breathing exercise, in hyperventilation syndrome 234
breathing reserve (BR) 73
breathlessness *see* dyspnoea
breath sounds, auscultation 123
Brims' decision tree 507
British Thoracic Society guidelines, pulmonary nodules 501, 502, 503, 504, 505
Brock model 455
bronchi
  airway resistance 30–31
  anastomotic problems
    fungal infections 407
    lung transplant complication 291
  anatomy 3–4, 358
  biopsy 127
  blood supply 115
  bronchoscopic assessment 127
  congenital anomalies 365, 367–370
  dilatation 361
  left main 3
  nonspecific reactive changes 10
  rare diseases 358–363
  right main 3
  stenosis 370
    in lung transplant recipients 133
  topographic anomalies 369–370
  tracheal ('pig bronchus') 369–370
bronchial arteries 3
bronchial artery embolisation (BAE) 298
bronchial-associated lymphoid tissue (BALT) lymphoma 678, 724
bronchial atresia 370
bronchial breathing 123
bronchial brushings 127, 208
bronchial carcinoma *see* lung cancer
bronchial epithelial cells 8–9
bronchial hyperresponsiveness (BHR) 77
  assessment *see* bronchial provocation testing (BPT)
  definition 77
  direct and indirect tests 77, 78

- bronchial provocation testing (BPT) 77–82
  - asthma 312–313
  - direct tests 77, 78–79, 82
    - contraindications 78–79
    - interpretation of results 79
    - standardisation 78
  - indications 77, 80
  - indirect tests 77, 80–82
    - cascade of effects 77, 78
- bronchial thermoplasty 131
- bronchial veins 3
- bronchial wall, weakness 370
- bronchial washings 127, 208
- bronchiectasis 353–357
  - aetiology 355, 357, 362
  - clinical features 353–354
    - chest pain 109
  - cystic fibrosis, respiratory physiotherapy for 234–235
  - definition 353
  - diagnosis 114, 353–354
  - diagnostic testing 354–355
  - diffuse, sleep-related hypoventilation 539
  - exacerbations 356–357
    - management 356–357
    - noninvasive ventilation 549
    - prevention 356
  - GORD association 413
  - HIV-infected patients 683
  - in inflammatory bowel disease 702, 705
  - long-term prognosis and outcomes 357
  - management
    - airway clearance 235, 355–356
    - antibiotics 356
    - chest physiotherapy 234–235, 236
    - corticosteroids/bronchodilators 356
    - eradication therapy 356
    - exercise 356
    - long-term oxygen therapy 270
    - long-term ventilation 270
    - prophylactic antibiotics 356
    - respiratory physiotherapy 234–235
    - stable patients 355
    - surgery 356
  - massive haemoptysis in 115
  - microbiology 355
  - nodular, nontuberculous mycobacteria causing 443
  - pathophysiology 353
  - in primary immunodeficiency 676
  - radiological subtypes 354
  - traction, HRCT 177
  - widespread, cystic fibrosis 730
- bronchioles 3
  - airway resistance 30–31
- bronchiolitis
  - in inflammatory bowel disease 702, 705
  - obliterative *see* obliterative bronchiolitis
  - post-transplant obliterative 413
  - in primary immunodeficiency 676
- bronchiolitis obliterans *see* obliterative bronchiolitis
- bronchiolitis obliterans syndrome (BOS) 291
- bronchitis 320–323
  - acute 320–321
  - aetiology/risk factors 320
  - chronic *see* chronic bronchitis
  - clinical features 321
  - definitions 320, 321, 325
  - diagnosis 321
  - eosinophilic 111, 322, 615–616
  - in inflammatory bowel disease 702, 705
  - non-asthmatic eosinophilic 322, 615–616
  - pathophysiology 321
  - persistent bacterial, sputum hypersecretion 114
  - prognosis 321, 322
  - treatment 321–322
- bronchoalveolar lavage (BAL) 7, 11, 13, 127–128, 138–144
  - cell counts 140
    - normal 140–141
    - smokers 141
  - cell type enumeration 140
  - complications 128, 139
  - definition 138
  - as diagnostic tool 141–144, 405
    - cellular patterns 142
  - eosinophilia 13, 142
  - fluid
    - collection containers 139
    - cytological findings 13, 140, 141–144
    - handling 139–140
    - milky/opaque 13
    - normal cytology 140–141
  - indications 138, 141, 143
  - laboratory processing 139–140, 405
  - lymphocytic pattern 142
    - CD4/CD8 ratio 143, 145
  - neutrophilic pattern 142
  - pepsin, in cystic fibrosis 414
  - procedure 127–128, 138–139
  - side-effects, and risk factors for 139
  - in specific diseases
    - adult pulmonary Langerhans cell histiocytosis 583
    - drug-induced respiratory disease 603
    - idiopathic pulmonary fibrosis 555
    - infections in neutropenia 405
    - interstitial lung disease 138, 141, 143, 145
    - lung infection in immunocompromised 389
    - opportunistic infections in neutropenia 405
    - primary immunodeficiency 678
    - pulmonary alveolar proteinosis 590
    - pulmonary vasculitis 639
    - sarcoidosis 565
  - total cell count 140
- bronchoarterial ratio 354
- broncho-aspiration, in connective tissue diseases 724

- bronchoconstriction
  - ACE inhibitors and AT1R blockers inducing 216
  - angiotensin II inducing 216
  - exercise-induced (EIB) 80, 310
  - reversal by β_2-agonists 344–345
- bronchodilators 344
  - adult pulmonary Langerhans cell histiocytosis 584
  - anticholinergic drugs 346
    - *see also* anticholinergic therapy
  - asthma 317, 344–346
  - β_2-adrenergic agonists *see* β_2-adrenergic agonists
  - bronchiectasis treatment 356
  - COPD 329, 344–346
    - exacerbation prevention 336–337
    - exacerbation treatment 334, 336
  - lymphangioleiomyomatosis 588
  - theophylline 347
  - *see also* specific bronchodilators
- bronchogenic carcinoma 453
  - *see also* lung cancer
- bronchogenic cyst 515
- bronchomalacia 370
- bronchomegaly 361
- bronchoplastic lobectomy 476, 477
- bronchopulmonary segments, anatomy 3
- bronchoscope, flexible 124, 125, 139
- bronchoscopic thermal vapour ablation (BTVA) 285
- bronchoscopy 124–131
  - advanced diagnostic procedures 128–130
  - BAL during 139
  - complications 128
  - equipment 124, 125
  - fluorescence 128–129
  - indications 124–125
  - mortality 128
  - patient preparation 125–126
  - procedure 126–127
  - sampling techniques 127–128, 208
  - sedation 126, 128
  - in specific diseases
    - drug-induced respiratory disease 603
    - lung abscess 280
    - lung infection in immunocompromised hosts 389
    - pulmonary carcinoids 492
    - pulmonary vasculitis 639
    - rare airway diseases 359
  - therapeutic 124–125, 130–131
  - virtual 134
- bronchospasm
  - catastrophic, drug-induced 609
  - drug-induced 598, 609
  - total lung capacity increase 84
- bronchus intermedius 3
- 'bronchus sign' 208
- brushing, bronchial 127, 208
- BTNL2 gene 563
- budesonide 345
  - side-effects 349
- building dampness 776
- BUILD trial 577
- bulbar disease, long-term ventilation 269
- bullae, spontaneous pneumothorax 667
- bupropion 263, 264
- burden of disease 757
- *Burkholderia cepacia* complex 733, 738
- byssinosis 752

C

- C1q deficiency 404
- C3 deficiency 404
- C5 deficiency 404
- C9 deficiency 404
- cachexia
  - COPD patients 245
  - palliative care 250–251
- caisson disease (decompression sickness) 783–784, 784–785
- calcific blue bodies 10
- calcium channel blockers 630, 634
- calcium oxalate crystals 10
- calcospherites 10
- cancer
  - lung *see* lung cancer
  - smoking and 259
  - *see also* specific tumour types
- *Candida* infection
  - cytological findings 12
  - detection 407
  - pneumonia
    - in neutropenia 405
    - post-transplant 407
- cannabis, spontaneous pneumothorax 666–667
- cannibalism 13
- CANPAP trial 530, 532
- CAP *see* community-acquired pneumonia (CAP)
- CAPACITY trial 576
- capillaries, giant 723
- capillaritis 640
- capsaicin 111, 113, 216
- carbocysteine, COPD exacerbation prevention 337
- carbol fuchsin stain 202
- carbon dioxide (CO_2)
  - diffusion coefficient 35
  - dissociation curve 39
  - end-tidal tension (P_{ETCO_2}) 41, 42, 43
  - output (V'_{CO_2}) 28, 29
  - P_{ACO_2} (alveolar tension) 28, 29, 34, 37
    - V'_A/Q' mismatch 38–39
  - P_{aCO_2} (arterial CO2 tension)
    - abnormal, causes 61
    - acid–base disorders 63, 64
    - acute respiratory failure (type 2) 293, 541
    - arterial pH and 63
    - blood gas analysis 60, 61
    - congestive heart failure 530
    - elevated, sleep-induced hypoventilation 535

    - high altitude and 780
    - hypercapnic respiratory failure 62
    - obesity hypoventilation syndrome 537
    - reference interval 61
  - retention 36, 37
  - V'_{CO_2}, V'_E and, ventilatory efficiency 28, 72–73, 75
  - ventilatory response to inhalation 41, 42–44, 46
- carbon dioxide inhalation test 42
- carbon monoxide (CO) 54
  - air pollution 773
  - alveolar uptake (K_{CO}) 54, 55, 56, 58
  - marker of inflammation and oxidative stress 190
  - testing, smoking exposure 264
  - transfer factor *see* transfer factor of the lung for carbon monoxide (T_{LCO})
- carboplatin chemotherapy, lung cancer
  - NSCLC 229, 467
  - SCLC 467
- carcinogens
  - genotoxic 453, 454
  - tobacco smoking 453
- carcinoid crisis 493
- carcinoid syndrome 491, 492
- carcinoid tumours
  - atypical 16
  - cytology 15–16
  - pulmonary *see* pulmonary carcinoids
- carcinomatous lymphangiitis 497–498
- cardiac chest pain 109
- cardiac congestion 297
- cardiac disease
  - cardiac drugs effect on lung *see* cardiac drugs; cardiovascular drugs
  - chest radiograph (normal) 156
  - diagnostic flowchart 696–698
  - in eosinophilic granulomatosis with polyangiitis 639
  - lung disease with 692–700
    - asthma 215, 216, 693
    - COPD *see* chronic obstructive pulmonary disease (COPD)
    - diagnostic flowchart 696–698
    - minimum requirement for diagnosis 696–698
    - pulmonary hypertension 693
  - uncovering lung disease in patients 694–696
  - *see also* cardiovascular disease
- cardiac drugs, effect on lungs
  - antiarrhythmics 698–699
  - β-blockers 218–220, 698
  - *see also* cardiovascular drugs
- cardiac evaluation, pre-operative 92, 93
- cardiac involvement, in sarcoidosis 566
- cardiac output 72, 526
- cardiac remodeling 219
- cardiogenic pulmonary oedema 294, 296, 297, 526
  - acute, noninvasive ventilation 546, 550
  - diagnosis and clinical features 294, 296, 297
  - drug-induced 607
- cardiogenic shock 298
- cardiomyopathy, obesity 720
- cardiopulmonary exercise testing (CPET) 70–76
  - bronchial responsiveness testing 80–81
  - contraindications 71
  - in COPD 70, 73, 74, 245
  - dyspnoea assessment 99, 100
  - exercise variables and indices 71–74
  - indications 70, 71
  - as prognostic evaluation 75
  - protocols 70–71
  - response patterns 74–75
    - cardiovascular response 75
    - pulmonary gas exchange 75
    - ventilatory response 74
  - therapeutic intervention evaluation 75
- cardiopulmonary reserve, assessment before lung resection 94, 95
- cardiorespiratory monitoring 523
- cardiothoracic index 156
- cardiotoxicity 597
- cardiovascular disease (CVD)
  - in asthma 215, 216, 693
  - as consequence of obstructive sleep apnoea 524–525
  - COPD and *see* chronic obstructive pulmonary disease (COPD)
  - drugs for *see* cardiovascular drugs
  - radiation-induced 488
  - smoking and 259
  - *see also* cardiac disease
- cardiovascular drugs, impact on lung 216–220, 698–699
  - ACE inhibitors and AT1R blockers 216–217
  - β-blockers 218–220, 698
  - statins 217–218
- cardiovascular response, exercise testing 75
- caregivers, bereavement 252
- carotid bodies 42, 44
- carotid chemoreceptor response *see* chemoreceptor response
- case–control design studies 757, 759, 762
- caspofungin 391
- catastrophic bronchospasm 609
- categorical scales 753, 754
- causation, assessment 765
  - criteria for evidence assessment 765
- cavitary lung disease 443
- CCR5 24
- CD4$^+$ T-cells 21, 22, 23
  - BAL fluid pattern 143, 145
  - in COPD 22, 23
  - counts, HIV-related immunocompromise 682, 686
  - *see also* T-cell(s) (T-lymphocytes)
- CD8$^+$ T-cells 21, 22, 23
  - BAL fluid pattern 143, 145
  - in COPD 22, 23
  - hypersensitivity pneumonitis 558
- CD68$^+$ cells 24

CD152 *see* CTLA4 pathway
cell block preparations, lung cytology 7, 8
cell death, mechanisms 26
cell-mediated immunity 404
  delayed, hypersensitivity pneumonitis 558
  see also T-cell(s) (T-lymphocytes)
cell types 8–10
central apnoea syndrome 523, 524
central hypoventilation syndromes
  congenital 539
  long-term ventilation 269–270
central nervous system (CNS), tuberculosis 434, 435–436, 687
central sleep apnoea (CSA) 529–534, 532, 533
  aetiology 529
  conditions with 533
  in congestive heart failure 530–532
  criteria for 530
  diagnosis 531–532
  idiopathic 529, 533
    treatment 533
  nasal CPAP for 526
  pathophysiology 529, 530
  prevalence 529, 530
  symptoms 530, 531
  treatment
    adaptive servoventilation and 267, 532, 533
    CPAP 532, 533
    in heart failure 532
  treatment-emergent 533
  see also Cheyne–Stokes respiration (CSR)
cerebral oedema, high-altitude 780, 781
cervical pleura 1
cervicothoracic CT, descending necrotising mediastinitis 672
cetuximab 465, 598
CF *see* cystic fibrosis (CF)
CFTR *see* cystic fibrosis transmembrane conductance regulator (CFTR)
CFTR modulators 735
Charcot–Leyden crystals 10
CHARGE syndrome 364
checkpoint inhibitors 227–230
  see also immune checkpoint inhibitors
cheese worker's lung 560
chemical(s), occupational asthma 749, 750
chemical pleurodesis 664
chemical pneumonitis 412
chemical worker's lung 560
chemokines 24
chemoradiation, lung cancer 472–473
  NSCLC 469
    preoperative 484
    stage III 483
SCLC 468
chemoreceptor(s)
  'central,' sites 42
  peripheral (carotid bodies) 42, 43
chemoreceptor response 41
  to carbon dioxide 42–44, 46
  to hypoxia 43, 44–46
chemotherapy 463–464
  adjuvant 464
  infectious pneumonia associated 707
  lung cancer 463, 464
    NSCLC 464, 469, 470
    SCLC 468, 486
  malignant mesothelioma 470, 511, 512
  neoadjuvant/induction 464, 484
  pulmonary carcinoids 492
  side-effects 464, 465, 603, 607
  see also specific chemotherapeutic agents
chemotherapy lung 603, 607
chest 1
  auscultation 123
  bone metastases 498–499, 507
  CT *see* computed tomography (CT)
  drains *see* chest tube drainage
  expansion, assessment 121
  inspection 120–121
  MRI *see* magnetic resonance imaging (MRI)
  normal radiograph 156
  normal transthoracic ultrasonography 163
  palpation 121–122
  percussion 122
  physiotherapy *see* respiratory physiotherapy
chest fluoroscopy 159
chest infections *see* respiratory infections
chest pain 108–109
  cardiac 109
  in GORD 701
  malignant pleural effusions 509
  neuralgic amyotrophy 653
  pathophysiology 108
  pleural effusion causing 509, 661
  pneumomediastinum 670
  pulmonary embolism 620
  rapid assessment 108
  risk stratification 620
  spontaneous pneumothorax 667
chest radiography 154–158, 159
  abnormal 295
    CT indications 171
  after thoracentesis 153
  basic techniques 154–155
  bedside 157
  digital 157–158
  dose and image quality 159
  dual energy 158
  good, key points 155
  indications 156, 157
  inspiratory–expiratory 157
  interpretation and reporting 154, 156, 157
  new developments 158
  normal, CT indications 171
  projections 155–157
  recommendations for use 155, 156
  rib suppression technique 158

  - in specific conditions 156, 157
    - acute eosinophilic pneumonia 616
    - acute respiratory failure 294
    - alveolar pneumonia 295
    - ARDS 300
    - asthma 313
    - atelectasis 295
    - bronchiectasis 354
    - chest pain 109
    - chronic eosinophilic pneumonia 617
    - drug-induced respiratory disease 599, 601–602
    - febrile neutropenia 708
    - H1N1 pneumonia 300
    - hypersensitivity pneumonitis 559
    - infiltrative pneumonia 295
    - lung abscess 279
    - lymphangioleiomyomatosis 586
    - malignant pleural effusions 510
    - mediastinal tumours 516
    - NTM infections 445
    - pleural effusion 295, 661
    - pleural infection 275, 276
    - *Pneumocystis jirovecii* pneumonia 684
    - pneumomediastinum 670
    - pneumonia 377, 378, 394, 684
    - pneumothorax 295
    - primary viral (influenza) pneumonia 394
    - pulmonary alveolar proteinosis 590
    - pulmonary carcinoids 491
    - pulmonary metastases, excavated 496, 497
    - pulmonary oedema 295
    - rare airway diseases 359
    - respiratory muscle weakness 654
    - sarcoidosis 565–566
    - silicosis 751
    - spontaneous pneumothorax 667, 668
    - tuberculosis 420, 440, 686
    - tuberculosis in HIV infection 686
  - temporal subtraction 158
- chest tightness, exertional dyspnoea in asthma 104
- chest tube(s) 277
- chest tube drainage
  - empyema 149, 277
  - lung abscess 280
  - medical thoracoscopy/pleuroscopy 148–149, 150
  - parapneumonic effusions 275
  - pleural infections 275, 277
  - spontaneous pneumothorax 668
- chest ultrasonography 146–147
  - nodules on diaphragm 148
  - pleural adhesions 146–147
  - *see also* transthoracic ultrasound (TUS)
- chest wall
  - compliance 48
    - calculation 52
  - congenital abnormalities 649–652
    - controversies 651
    - pathogenesis 649
    - surgical treatment 650–651
    - *see also* pectus carinatum (PC); pectus excavatum (PE)
  - deformities and scars 120, 121
  - inspection 120
  - mass, transthoracic ultrasound 164
  - pain 109
  - pressure–volume curves 84
  - resistance 51
  - sarcomas 507
    - diagnosis, imaging 510
    - prognosis 508
    - treatment 512
  - transthoracic ultrasound 162, 163
  - tumours *see* chest wall tumours
- chest wall disorders 649–652
  - congenital *see under* chest wall
  - hypercapnic respiratory failure due to 543
  - management
    - long-term ventilation 268
    - respiratory physiotherapy 236
  - pathogenesis 649–650
  - sleep-related hypoventilation syndromes 538
  - transthoracic ultrasound 164
- chest wall tumours
  - benign 506
  - diagnosis 509
    - imaging 510
  - malignant 506–513
    - metastatic 498–499, 507
    - primary 506
  - prognosis 507–508
  - types 507
- Cheyne–Stokes respiration (CSR) 523, 529, 530
  - in congestive heart failure 530–532
  - criteria for 530
  - diagnosis 531–532
  - pathophysiology 530
  - treatment, in heart failure 532
  - *see also* central sleep apnoea (CSA)
- Chicago classification 702, 703
- children
  - air pollution hazards 771
  - asthma management 316
  - influenza complications 395
  - pulmonary tuberculosis 418
- Chi-squared test 769
- *Chlamydophila pneumoniae* diagnosis
  - diagnostic approach 195
  - serological tests 198
- chloride, sweat 728, 729, 731
- chloride channel 727–728
- chloride ions 64, 65
  - loss, acid–base disorder 64, 65, 66
- 2-chloro-deoxyadenosine (cladribine) 584
- choanal atresia 364
  - bilateral 364
- choanal stenosis 364
- chondroid hamartochondromas 18
- choriocarcinoma 17

- chronic airway inflammation *see* airway inflammation, chronic
- chronic bronchitis 321–322, 325
  - in COPD 325
    - management 115
  - definition 321, 325
  - simple (without airflow obstruction) 325
  - total lung capacity 84
  - *see also* chronic obstructive pulmonary disease (COPD)
- chronic cough *see* cough, chronic
- chronic eosinophilic pneumonia 616–617
- chronic granulomatous disease (CGD) 403
- chronic heart failure (CHF)
  - dyspnoea 103
  - *see also* heart failure
- chronic lung allograft dysfunction (CLAD) 290, 291
- chronic lung diseases *see* chronic pulmonary diseases
- chronic mountain sickness 782
- chronic myelomonocytic leukaemia 17
- chronic obstructive pulmonary disease (COPD) 324–331
  - acute exacerbation *see* acute exacerbations of COPD (AECOPD)
  - acute-on-chronic respiratory failure 543–544
  - aetiology 20, 324–325
  - airflow obstruction 309, 314, 325, 327
    - exacerbation diagnosis 334
  - air pollution effect 772
  - airway inflammation 188, 189, 322, 325, 694
    - chronic 20, 322, 339, 340, 341
    - inflammatory cells 20–21, 322, 325
    - patterns 322
    - systemic inflammation and 339, 340, 341
  - altitude effects 782
  - in α_1-antitrypsin deficiency (AATD) 745, 746
  - asthma comorbid with 315, 333
  - asthma *vs* 308, 309, 310, 312, 313
    - ancillary tests 315
    - lung function tests and symptoms 314–315
  - biomarkers
    - exhaled breath condensate 191, 192
    - sputum 189
  - body composition changes 245
  - cachexia 245
  - cardiovascular disease in 215, 216, 339, 340, 692–693
    - clinical implications 694–696
    - common risk factors 693
    - COPD exacerbations 333, 694
    - COPD underdiagnosis 695–696
    - diagnosis of COPD in heart disease 694–696
    - diagnosis of heart disease in 696
    - heart failure 218, 692–693, 694
    - ischaemic heart disease 692, 693–694
    - pathophysiology 693–694
    - systemic inflammatory response 693–694
  - characteristics 258
  - chronic bronchitis in 325
    - management 115
    - without airflow obstruction, COPD prediction 322
  - chronic inflammation 20, 325, 339, 340, 341
  - as ‘chronic systemic inflammatory syndrome’ 339, 341
  - classification 325–326, 328–329
  - clinical features 245–246, 314, 326, 327–328, 695
    - deterioration 328
    - dyspnoea 97, 101, 105, 245–246, 327, 695
    - exacerbations 334
    - fatigue 246
  - clinical presentation 327
  - coal mining and 752
  - comorbidities 215, 325
    - asthma 315, 333
    - cardiovascular disease *see above*
    - chronic bronchitis 115, 325
    - emphysema 325
    - extrapulmonary 339, 340
    - HIV infection 688–689
    - impact on patient care 341
    - management 330, 342
    - metabolic disorders 340
    - obesity 245, 539, 718–719
    - obstructive sleep apnoea 254
    - pathophysiology 340, 341
    - primary immunodeficiency 676
    - Sjögren syndrome 724
    - systemic effects 340, 341
    - therapeutic implications 341–342
  - cytokines 340, 341
  - definitions 324, 718
  - diagnosis and assessment 325–327, 341
    - ancillary tests 315
    - in cardiac disease 694–696
    - early diagnosis important 105
    - FEV_1 decline rate 327, 328
    - FEV_1/VC ratio 325
    - misdiagnosis in heart disease 695
    - spirometric severity 326
    - spirometry, in heart disease 695
  - diving and 785
  - dyspnoea as mortality predictor 97
  - dyspnoea pathophysiology 101
  - emphysema *see* emphysema
  - endothelial dysfunction 340
  - eosinophilic 25, 322
  - epidemiology 324
  - exacerbations *see* chronic obstructive pulmonary disease (COPD) exacerbations
  - exercise intolerance 70, 73, 74, 101, 245
    - obesity and 718
  - exercise levels 241, 246
  - exercise testing 70, 245
    - as prognostic indicator 75
  - exercise training 234, 240, 244–245

  extrapulmonary consequences 244–245, 339–343
  genetics 324
  GOLD groups (groups A-D) 326, 328–329
  GORD association 414
  high altitude 782
  histology 309
  HIV infection association 688–689
  hospital admissions, and risks 246
  immune response and inflammation 20–26, 339, 340, 341
    airway inflammation *see above*
    B-cells 21–23
    chronic inflammation 20, 325, 339, 340, 341
    dendritic cells 24
    eosinophils 25, 322
    inflammatory cell types 21, 322, 325
    inflammatory mediators 21, 340
    macrophages 21, 24
    neutrophils 21, 23, 25
    NK cells 23
    systemic inflammation 339, 340, 341
    T-cells 21, 22, 322
    type-1 innate lymphoid cells 23–24
  immunohistochemistry 22
  lung hyperinflation 718
  lung volumes 718
  management *see* chronic obstructive pulmonary disease (COPD) management
  mild
    exertional dyspnoea 105
    pathophysiology 105
  misdiagnosis
    in heart disease 695, 696
    in obesity 718
  monitoring 328
  mortality 336
  natural history 327–328
  in obesity 245, 539, 718–719
  pathogenesis/progression 21, 22, 23, 24, 25, 26
  pathophysiology 324–325
  phenotypes 20, 325, 339
    exacerbations 332–334
  physical activity levels 241, 246
  predictors, of development 322, 324
  prevalence 258
  in primary immunodeficiency 676
  prognosis 330
  respiratory mechanics 32–33
  risk factors 324
    air pollution 324
    smoking 258, 261, 324, 340
  screening 105
  severe
    clinical features 327
    high altitude and 782
  severe exacerbations *see* chronic obstructive pulmonary disease (COPD) exacerbations
  severity classification 325–326
  skeletal muscle dysfunction 244–245
  sleep-related hypoventilation 539
  smoking cessation 263, 328
  smoking continuation 261
  sputum neutrophils 188, 189
  systemic consequences 241, 244
  systemic pharmacotherapy impact on 215–216
    ACE inhibitors and AT1R blockers 216, 217
    beta-blockers 218–220
    glitazones 220
    GLP-1 receptor agonists 220–221
    ROCK inhibitors 222
    statins effect 217–218
    sulphonylureas 220
  T-cell increase 21, 24
  underdiagnosis in heart disease 695, 696
  vaccinations in 328, 336
  wasted ventilation, $V'_{\mathrm{E}}/V'_{\mathrm{CO_2}}$ slope 73
chronic obstructive pulmonary disease (COPD) exacerbations 328, 332–338
  acute *see* acute exacerbations of COPD (AECOPD)
  aetiology 328, 332–334
    air pollution 772
    bacterial/viral infections 25–26, 328, 333, 335
    infective 25–26, 328, 333, 335
    noninfective 333, 772
  cardiac muscle injury/strain and 694
  classification (mild, moderate, severe) 330
  definition 328, 332
  diagnosis 334
  eosinophilic 25, 333, 334, 336
  frequency and impact 332
  heart disease and 333, 694
  hospital admission 335, 336
  immune response 25
  inflammatory 333
  inflammatory mediators 340
  mortality 336
  outcomes 336
  pauci-inflammatory 334
  pharmacotherapy reducing 329, 335, 348
  phenotype-directed treatment 337
  phenotypes 332–334
  predictors 328, 332
  prevention 336–337, 342, 348
  pulmonary rehabilitation indication 243, 246
  respiratory failure 295–296, 543–544
  risk classification and antibiotics 335
  risk factors for treatment failure 336
  severe 328, 332
    treatment 330, 335
  treatment 115, 330, 334–336, 342, 348, 351
    antibiotics 335
    β-blockers 342
    noninvasive ventilation 544, 546, 547, 548
    oxygen therapy 336
    pharmacotherapy 329, 335, 336, 348

    - *see also* chronic obstructive pulmonary disease (COPD) management
  - very severe, treatment 335
- chronic obstructive pulmonary disease (COPD) management 328–330
  - anticholinergic drugs 346
  - β_2-adrenergic agonists 329, 344–345
  - bronchoscopic 131
  - as chronic systemic inflammatory syndrome 341–342
  - of comorbidities 330, 341–342
  - corticosteroids 348, 349
  - environmental exposure reduction 328, 336
  - of exacerbations *see* chronic obstructive pulmonary disease (COPD) exacerbations
  - exercise training 234, 240, 244–245
    - *see also* pulmonary rehabilitation
  - goals 328
  - by GOLD group 328–329
  - long-acting muscarinic receptor antagonist (LAMA) 329, 346
  - long-term oxygen therapy 254, 270, 329
  - long-term ventilation 270
  - lung transplantation 288, 290, 329
  - non-pharmacological 329–330
  - palliative care 330
  - pharmacotherapy 328–329, 344–352
  - pulmonary rehabilitation *see* pulmonary rehabilitation
  - respiratory physiotherapy 233–234
  - roflumilast 351
  - short-burst oxygen therapy 254
  - statins 342
  - surgery 329
  - theophylline 347
  - triple therapy 329
  - vaccinations 328, 336
- chronic pulmonary diseases
  - exercise testing 70, 71
  - pulmonary hypertension due to 629, 630
  - *see also* specific diseases
- chronic renal failure, tuberculosis risk 429–430
- chronic respiratory failure (CRF) 538, 541
- chronic rhinitis, asthma association 315
- chronic rhinosinusitis (CRS) 304, 305–307
  - clinical features 306
  - in cystic fibrosis 730
  - diagnosis and differential diagnosis 306
  - endotypes 306
  - epidemiology 305–306
  - inflammatory response 306
  - management 307, 743
  - with nasal polyps (CRSwNP) 305–306, 307
  - primary ciliary dyskinesia 741
- chronic systemic inflammatory syndrome 339, 341
  - components 341
- chronic thromboembolic pulmonary hypertension (CTEPH) 628, 629, 630, 631
  - diagnosis 631, 633
  - treatment 636
- chronic ventilatory failure, long-term oxygen therapy 254
- Churg–Strauss syndrome 637
  - *see also* eosinophilic granulomatosis with polyangiitis (EGPA)
- chylothorax 664
- cigarettes 257, 261, 263, 453, 454
  - *see also* smoking
- cigarette smoke 453, 454
- cigarette smoking *see* smoking
- cilia 740, 741
  - '9+2' structure 741
  - coordinated beating 740, 741
  - dyskinetic 740
  - loss 11
  - motile 740, 741
  - transmission electron microscopy 742
- ciliated epithelial cells 740, 741
- ciliocytophthoria 11
- ciprofloxacin therapy
  - COPD exacerbations 335
  - pneumonia 381
    - hospital-acquired 386
  - pulmonary tuberculosis 422
- cirrhosis 701, 704, 745
  - pleural effusion secondary to 661
- cisplatin chemotherapy
  - lung cancer 466
    - NSCLC 469
    - SCLC 468, 486
  - malignant mesothelioma 470
- cladribine 584
- clarithromycin therapy
  - nontuberculous mycobacterial infections 445
  - pulmonary tuberculosis 424
- clean air, principles 772
- cleft sternum 649
- clindamycin, *Pneumocystis jirovecii* pneumonia 684
- Clinical and Functional Translation of CFTR 728
- clinical studies 757, 758
- clofazimine therapy, pulmonary tuberculosis 424
- club cells 9
- CMV syndrome 406
  - *see also* cytomegalovirus (CMV) infection
- coaching programmes 241
- coagulation disorders, haemoptysis due to 115
- coal, indoor combustion 776
- coal dust exposure 751
- coal workers' pneumoconiosis (CWP) 750, 751
- cognitive behaviour therapy (CBT) 241
- coherence, evidence of causation 765
- cohort studies 757, 758, 761, 762
- colchicine 576
- cold abscess 436
- cold air, for indirect bronchial provocation testing 81, 82
- cold water immersion 784
- collateral ventilation (CV) 283

colon, CF-related disease 736
combined immunodeficiencies, infections 676
combined population attributable risk (PAR) 764
common cold 304, 372
common variable immunodeficiency (CVID) 401, 679
    diagnosis, criteria 677
community-acquired pleural infection 274, 275, 379
community-acquired pneumonia (CAP) 296–297, 377
    acute respiratory failure in 294, 296–297
    antibiotic resistance 379
    bacteriology 274, 275, 296, 379
    causative agents 296
    clinical features 378
    clinical stability, criteria 381, 382
    definition/criteria 296–297
    diagnosis 296, 378–379
        blood cultures 196, 379
    differential diagnosis 379
    epidemiology 377–378
    HIV-infected patients 683
    hospitalised, management 380, 381
    management 380–381
        respiratory physiotherapy 236
    organ dysfunction, minor criteria 379–380
    respiratory emergency 296–297
    risk of mortality, prediction 379, 380
    severe 379
        definition/criteria 297
        management, antibiotics 381
    severity assessment 379–380
compensation, occupational diseases 752
complement
    activation, in COPD 22–23
    deficiency 404
compost lung 560
computed tomography (CT) 169–171
    dual-energy 170, 171
    HRCT *see* high-resolution computed tomography (HRCT)
    indications 169, 170–171
    low-dose 170
        lung cancer screening 454–455
        solitary pulmonary nodules 455
    MRI *vs* 169, 171
    for percutaneous needle aspiration 209
    PET with *see* positron emission tomography (PET)/CT
    prone position 175
    in specific conditions
        chest pain investigation 109
        chronic rhinosinusitis 306
        descending necrotising mediastinitis 672
        empyema 276, 279
        endobronchial metastasis vs lung cancer 497
        granulomatosis with polyangiitis 640, 641
        lung abscess 279
        lung cancer 456, 460, 497
        lung cancer staging 457
        lung disease diagnosis, elements 171
        lung infection in immunocompromised 389
        malignant pleural effusions 510
        mediastinal tumours 516–517
        pleural effusion 510, 661
        pneumomediastinum 670
        pulmonary nodules 501, 502, 505
        rare airway diseases 359
        sarcoidosis 565, 566
        severe haemoptysis 298
        solitary pulmonary nodules 455
        spontaneous pneumothorax 667
    spiral (helical) 169, 170, 171
        advantages 170
        multislice 169, 170, 175, 179
        radiation dose 170
    technical developments 169, 170, 171
    thin-section (high-resolution) 170
        see also high-resolution computed tomography (HRCT)
computed tomography (CT) angiography (CTA)
    contraindications 182, 625
    pulmonary arteriovenous malformations 648
    pulmonary embolism 182, 623–624, 624–625
        accuracy improvements 625–626
confidence interval 761, 765, 768–769
    calculation 768–769
confounding 766
congenital airway disease (CAD) 364–371
    laryngeal 365–367
    morbidity 364
    nasopharyngeal 364–365
    trachea and bronchial tree 365, 367–370
congenital central hypoventilation syndrome (CCHS) 266, 539
    long-term ventilation 269
congenital heart disease, right-to-left shunt 37
congenital subglottic stenosis 366
congestive heart failure (CHF)
    central sleep apnoea 530–532
    Cheyne–Stokes respiration 530–532
    exercise intolerance 70, 74
    exercise testing as prognostic indicator 75
    nasal CPAP in 526
    spirometry interpretation in 695–696
    see also heart failure
connective tissue diseases (CTDs) 722–726
    clinical features 723–724
    differential diagnosis 725
    epidemiology 722
    haemoptysis 115
    investigations 724–725
    management 725
    severity assessment 724–725
consolidation, lung
    drug-induced respiratory disease 602, 603
    eosinophilic granulomatosis with polyangiitis 640
    ultrasound of 166–167
constant work rate (CWR) tests 71, 75

contingency table 760, 767
continuous diaphragm sign 670
continuous positive airway pressure (CPAP) therapy
  acute cardiogenic pulmonary oedema 550
  central sleep apnoea 532
  Cheyne–Stokes respiration 532
  community-acquired pneumonia 380
  hypoxaemic respiratory failure 542
  neuromuscular disease patients 658
  obesity and pulmonary hypertension 720
  obesity hypoventilation syndrome 269–270, 538, 549
  obstructive sleep apnoea 525–527
    in obesity 719
    treatment-emergent central sleep apnoea 533
  oxygen therapy and 255
continuous scales 753, 754
COPD *see* chronic obstructive pulmonary disease (COPD)
coronavirus infections 397, 398
corpora amylacea 10
cor pulmonale 327
correlation 769
corticosteroid-sparing therapy, asthma 351
corticosteroid therapy 348–349
  adult pulmonary Langerhans cell histiocytosis 584
  amiodarone pulmonary toxicity 607
  ARDS 302
  asthma 348
  clinical use 348
  CNS tuberculosis 435
  drug-induced pneumonitis 606
  drug-induced respiratory disease 606, 607–608, 610–611
  eosinophilic bronchitis 615–616
  eosinophilic pneumonia 617
  extrapulmonary tuberculosis 434, 435
  hypereosinophilic syndrome 618
  hypersensitivity pneumonitis 561
  idiopathic interstitial pneumonia 574–575
  inhaled *see* inhaled corticosteroids (ICS)
  intravenous, asthma 348
  mode of action 348
  oral/systemic
    asthma 348
    COPD exacerbations 330, 336
    side-effects 349
  pulmonary alveolar proteinosis 591
  sarcoidosis 567
  severe influenza 395
  side-effects 348–349, 574
  tapering 574
  see also glucocorticosteroids; specific corticosteroids
corticosteroid withdrawal syndrome 349
costochondritis 109
costodiaphragmatic recesses 1
costomediastinal recess 1
costovertebral pleura 1
co-trimoxazole
  Pneumocystis jirovecii pneumonia 684, 685
  prophylactic, in pulmonary vasculitis 644
  cough 110–116
  ACE inhibitors and 609
  acute 110
  acute bronchitis 320, 321
  asthmatic 111
  chronic 110, 111–114
    bronchiectasis 353
    COPD 695
    diagnosis 111
    eosinophilic bronchitis 615
    epidemiology 111
    management 111–112, 114
    non-asthmatic eosinophilic bronchitis 322
    risk factors 111, 112
    sputum eosinophil count 188
    sputum hypersecretion 114–115
  chronic bronchitis 321
  daily wet 741
  effectiveness 658
    assessment 658
    respiratory physiotherapy help in COPD 234
  environmental tobacco smoke exposure 776
  in GORD 701, 702
  idiopathic interstitial pneumonias 570
  influenza 394
  lung cancer 456
  malignant pleural effusions (MPEs) 508–509
  pathophysiology 110
  peak flow 658
  productive
    chronic bronchitis 321, 325
    COPD 325, 327
  reflux 111
  smoker's 325
  'TOF' 368
cough challenge 111
  citric acid 114
cough hypersensitivity syndrome 111
cough reflex
  defective 110
  sensitivity to environmental stimuli 111
cough syncope 110
counselling, smoking cessation 262
Cowdry type A nuclear inclusions 11, 12
Cowdry type B inclusions 11
Coxiella, community-acquired pneumonia 379
Cox proportional hazards model 769
Coxsackie B virus infection 109
CPAP *see* continuous positive airway pressure (CPAP) therapy
CR3 (CD18/CD11b) deficiency 404
crackles 123
cranial irradiation, prophylactic, SCLC 468, 486
craniofacial anomalies 365
'crazy paving' pattern 590
CRB65 score 379, 380

C-reactive protein (CRP) 334, 340, 341
creatinine, pneumonia 379
Creola bodies 11
cricoarytenoid arthritis 724
critical closing pressure (PCRIT) 523, 524, 526
critically-ill patients, respiratory physiotherapy 238
crizotinib 449, 450, 467
Crohn's disease 436, 705
crossover studies 759
crossover trials 757
cross-sectional epidemiological studies 757, 758
cryobiopsy 130, 208
cryo-bronchial lung biopsy 128, 130
cryoprobes 130, 131, 133
Cryptococcus infection, cytological findings 12
cryptogenic organising pneumonia (COP) 569, 574, 723
  haematological disease association 714
  in primary antibody deficiency (PAD) 677, 678
  see also idiopathic interstitial pneumonias (IIPs)
CSA *see* central sleep apnoea (CSA)
CSR/CSA syndrome 529
  in congestive heart failure 530–532
  see also central sleep apnoea (CSA)
CT *see* computed tomography (CT)
CTA *see* computed tomography (CT) angiography (CTA)
CTLA4 pathway 227–228, 467
  blockade 227–228, 467
culture, nontuberculous mycobacteria (NTM) 444
culture media, for mycobacteria 203
culture techniques 194, 196
  respiratory tract pathogens 194, 196, 198
  sputum 196
  tuberculosis diagnosis 203
    drug resistance 204–205
    pulmonary TB 420
cumulative incidence 755
cumulative incidence ratio 761
CURB65 score 379
Curschmann's spirals 10
Cushing's syndrome 456, 491, 492, 493
CVID *see* common variable immunodeficiency (CVID)
CXCL-5 25
CXCL7 25
CXCL-8 25
cycle ergometer, tests on 71, 81
cyclophosphamide therapy 575
  adverse effects 610
  idiopathic pulmonary fibrosis 575
  metabolism in lung cells 598
  pulmonary vasculitis 643
cycloserine therapy, pulmonary tuberculosis 423
cyclosporine therapy
  asthma 351
  idiopathic pulmonary fibrosis 575
CYP2C allele 604
cyst(s)
  bronchogenic 515
  enterogenic 515
  laryngeal 367
  lung *see* lung cysts
  mediastinal *see* mediastinal cysts
  pleuropericardial 515
  thin-walled, adult pulmonary Langerhans cell histiocytosis 582, 583
  thymic 515
cysteinyl-leukotrienes 349
cystic fibrosis (CF) 727–739
  bronchiectasis, respiratory physiotherapy for 234–235
  cascade screening 730
  diagnosis 728, 730–731
    in adults 728
    sputum biomarkers 189
  diagnostic criteria 730
  exercise intolerance 70
  exercise testing as prognostic indicator 75
  gastrointestinal disease 414, 731
  genetics 727–728
  GORD and reflux association 414
  late presentation 728, 730
  lung disease in 730, 731
  management 731, 735
    airway clearance 235, 732
    antimicrobials 731, 732, 733
    CFTR modulators 735
    by disease stage 732–734
    drug development problems 735
    end-of-life 738
    hygiene measures 235
    long-term ventilation 270
    of lung disease 731, 732–734, 733, 734
    lung transplantation 288, 290, 738
    noninvasive ventilation 549
    by organ system disease 736–737
    physiotherapy 234–235, 731
    postural drainage 235
  mucus composition 114
  organ system disease 735, 736–737
  pathophysiology 727–728
  phenotypic expression 728
  prevalence 727
  pulmonary exacerbations 731
  respiratory infections in 728, 730, 731
    management 731, 732, 733, 734
  screening 355, 728
  sleep-related hypoventilation 539
  survival/prognosis 728, 738
cystic fibrosis transmembrane conductance regulator (CFTR) 727
  corrector and potentiator drugs 735
  DNA testing 731
  functions 727–728
  gene mutation classes 728, 729, 731
  modulators 735
cytisine 263

cytokines
  asthma 322
  COPD 21, 22, 23, 26, 340, 341
  idiopathic interstitial pneumonias 569
cytology 7–19
  general findings 8–10
  investigations on samples 9
  nonspecific reactive changes of respiratory epithelium 10–14
  reactive features 7
  routine preparations 8
  in specific disorders
    benign non-neoplastic disorders 12–14
    germ cell tumours 17
    lung tumours 14–16
    lymphoproliferative/myeloid disorders 16–17
    malignant pleural effusions 510
    mesenchymal tumours 18
    pulmonary infections 11–12
    thymomas 17
  staining procedures 7–8
cytomegalovirus (CMV) infection
  conditions caused by 406
  cytological changes 11
  in neutropenia 405
  pneumonia 390
  post-transplant infection 406–407
  primary 407
  prophylaxis 390
  reactivation, after transplant 407
  reinfection 407
  syndrome 406
  treatment 390
cytospin 8
cytotoxic T-lymphocyte-associated antigen 4 *see* CTLA4 pathway

D
damage-associated molecular patterns (DAMPs) 26
dampness, exposure 776
dapsone, *Pneumocystis* pneumonia management 684, 685
dasatinib
  pleural effusion due to 712
  pulmonary arterial hypertension due to 629
daytime sleepiness 522, 530, 531, 533
D-dimer measurement 621, 623
dead space ventilation, pulmonary embolism 624
DECAF score 330
decompression sickness 783–784, 784–785
'decontamination,' samples for nonmycobacterial organisms 202
deep vein thrombosis (DVT) 621, 625
defence systems 20–27
  see also immune response
Dejours hypoxia-withdrawal test 41, 45–46
dendritic cells 24
  in COPD 24
  types (myeloid, plasmacytoid) 24
depression 241, 250
dermatophagoides farinae-1 26
descending necrotising mediastinitis (DNM) 671
  clinical/radiological signs 672
  diagnostic criteria 671
  epidemiology 671
  mortality 671, 672
  pathogens involved 672
  phases (I-III) 672
  route of diffusion 672
  treatment 673–674
    close-watch care 673
desquamative interstitial pneumonia (DIP) 13, 569
  corticosteroid therapy 574
  see also idiopathic interstitial pneumonias (IIPs)
DETECT study 725
development of respiratory system 6
diabetes insipidus 582
diabetes mellitus
  antihypoglycaemic drugs, impact in COPD/asthma 220–222
  in asthma and COPD 215, 216, 220
diagnosis of lung disease
  algorithm 119
  procedures 124–209
  symptoms and physical examination 118, 119
  see also specific procedures and diseases
  diaphragm
  anatomy 5–6
  chest radiograph (normal) 156
  dysfunction 294
  EMG 655, 656, 657
  evaluation 655–656
  innervation 108
  irritation, referred pain 108
  neuromuscular diseases and *see* neuromuscular diseases
  nodules on 148
  pacing 658
  weakness 654
    evaluation 654, 655–656
    management 656–657, 658
    sleep disordered breathing 657
    see also neuromuscular diseases
diaphragmatic pleura 1
diesel vehicles 774
dietary therapy, in obesity 720, 721
difference, exposure–health outcome relationship 760, 763, 764
Diff-Quik staining procedure 7, 8, 140
diffuse alveolar damage (DAD) 11
  drug-induced 597
diffuse alveolar haemorrhage (DAH) 638
  acute respiratory failure due to 294, 296, 297
  drug-induced 599, 604, 608
  granulomatosis with polyangiitis 640
  in haematological disease 714
  microscopic polyangiitis 641

  - vasculitis causing 297, 638, 640, 641
- diffuse interstitial lung disease (DILD)
  - diagnosis
    - HRCT and histology relationship 177
    - HRCT patterns 175, 176, 177–178
    - lung biopsy 176
  - *K*CO and *T*LCO 58
  - monitoring, by HRCT 178–179
  - positive predictive value (PPV), HRCT 176
  - prognosis prediction, by HRCT 178
  - prone CT 175
  - *see also* interstitial lung disease (ILD)
- diffuse parenchymal lung diseases 553–619
  - *see also* interstitial lung disease (ILD)
- diffusing capacity of lung for carbon monoxide (*D*LCO) *see* transfer factor of the lung for carbon monoxide (*T*LCO; *D*LCO)
- diffusion equilibrium 36
- diffusion impairment 35–36
- diffusive–perfusive conductance ratio 36
- digital radiography (DR) 157–158
- digital tomosynthesis 158
- digital ulcer 723
- dimethylarginine, asymmetric 191
- dipeptidyl peptidase (DPP)-4 220–221
- DIRD *see* drug-induced respiratory disease (DIRD)
- direct immunofluorescence (DIF) 197
- distal contractile integral (DCI) 703
- diving
  - physiological consequences 784
  - pre-existing lung disease 785
  - pressure changes 779
- diving-related disease 783–784, 784–785
- *D*LCO *see* transfer factor of the lung for carbon monoxide (*T*LCO; *D*LCO)
- DNA, radiotherapy actions 482
- DNA adducts 453, 454
- DNAse 277, 356, 664
- DNA sequencing, *Mycobacterium tuberculosis* complex 205
- docetaxel chemotherapy
  - checkpoint inhibitors *vs*, NSCLC 228
  - lung cancer 466
  - NSCLC 228, 469
- dosimeter method, bronchial provocation test 78, 79
- DOTS (directly observed treatment, short course) 426
- Down syndrome 365, 527
- drug(s)
  - metabolism, in lung tissues 598
  - resistance
    - antibiotics *see* antibiotics
    - anti-tuberculosis drugs *see* anti-tuberculosis drugs
  - sensitivity testing, tuberculosis 204–205, 390, 419, 420, 421
  - withdrawal, drug-induced respiratory disease and 596, 597, 605
- drug addicts 598
- drug-induced airway compromise 596, 597
- drug-induced respiratory disease (DIRD) 595–611
  - acute/serious/life threatening 596, 600, 611
  - airway involvement 608–609
  - asthma and bronchospasm due to 598, 609
  - biomarkers 605
  - clinical presentation 596, 605
  - diagnosis 604–605
  - diagnosis by exclusion 596
  - diagnostic workup 599, 603–604
    - BAL 603
    - fibreoptic bronchoscopy 603
    - imaging, patterns 599, 601–602, 603
    - other tests used 604
    - pulmonary function 603
  - disordered breathing during sleep 610
  - drug administration route 596
  - drugs causing 596, 597, 599
    - imaging patterns 599, 601–602, 603
  - epidemiology 599
  - general features 596–597
  - interstitial lung disease due to 599, 606
  - lone breathlessness 610
  - management
    - checklist 600
    - corticosteroid treatment 606, 607–608, 610–611
  - methaemoglobinaemia 610
  - parenchymal 606–608
    - acute pneumonitis 606
    - amiodarone pulmonary toxicity 603, 606–607
    - chemotherapy lung 607
    - diffuse alveolar haemorrhage 608
    - organising pneumonia 607–608
    - pulmonary fibrosis 608
    - pulmonary infiltrates and eosinophilia 606, 616
    - pulmonary oedema 607
    - sarcoid-like endothoracic involvement 608
  - pathology 604
  - pleural pathology 609–610
  - pulmonary vasculopathy 610
  - timing of drug use 605
  - withdrawal of drugs 596, 597, 605
- drug rash with eosinophilia and systemic symptoms (DRESS) 596, 606
- drugs of abuse 596, 598
  - pulmonary hypertension and 610
- drug susceptibility testing (DST), tuberculosis 204–205, 390, 419, 420, 421
- dry powder inhalers (DPIs) 212, 213
- dual energy chest radiography 158
- dual energy CT 170, 171
- dual-mode ventilators 267
- Duchenne muscular dystrophy 268
  - respiratory failure 653
  - sleep-related hypoventilation syndromes 538, 539
  - *see also* neuromuscular diseases (NMD)
- durvalumab 230, 467, 469

- dusts, inhalational injury 750, 751, 752
- ‘dying spells’ 368
- dynamic hyperinflation 73
- dynamic lung volume 83, 88
- dynein 740, 741
- dysphagia 701, 702, 703
- dyspnoea 97–107
  - assessment 117, 118, 119
    - evaluation during physical tasks 99–100
  - Borg scale 99–100
  - causes 117
  - definition 97
  - exertional 98, 99, 100
    - adult pulmonary Langerhans cell histiocytosis 582
    - chronic, idiopathic pulmonary fibrosis 554
    - in connective tissue diseases 723
    - COPD 101
    - evaluation 99–100
    - lymphangioleiomyomatosis 586
    - management 99, 105–106
    - neurophysiological basis 98
    - in obesity 717
    - *Pneumocystis jirovecii* pneumonia 684
    - pulmonary vasculitis 638
    - in specific diseases 101, 102, 103, 104, 105
    - *see also* dyspnoea, pathophysiology
  - lone, drug-induced 610
  - management
    - effects of interventions 105–106
    - respiratory physiotherapy 233–234
  - MRC dyspnoea scale 99
  - neurophysiological basis 97, 98
  - nocturnal 531
    - *see also* central sleep apnoea (CSA)
  - onset, and differential diagnosis 118
  - palliative care 250
  - pathophysiology 101–105
    - airway obstruction in asymptomatic patients 105
    - asthma 104
    - chronic heart failure 103
    - COPD 101, 105
    - interstitial lung disease 102–103
    - mild COPD 105
    - neuromuscular disorders 101–102
    - obesity 103–104
    - pulmonary arterial hypertension 104–105
  - perceived as sense of air hunger 100
  - perceived as sense of effort 100
  - physiology 100
  - progressive, investigations 555
  - in specific conditions
    - acute respiratory failure 293
    - asthma 104, 309
    - COPD 97, 101, 105, 245–246, 327, 695
    - heart failure 695
    - hepatopulmonary syndrome 702, 704, 705
    - idiopathic interstitial pneumonias 570
    - malignant pleural effusions 506, 508–509
    - neuromuscular diseases 653
    - pleural effusion 506, 508–509, 661
    - pneumonia 378
    - rare airway diseases 359
    - respiratory muscle weakness 654
    - severe COPD exacerbations 336
    - sleep-related hypoventilation syndromes 536
    - spontaneous pneumothorax 667
  - sudden-onset, pulmonary embolism 620
  - visual analogue scale 100
- dyspnoea threshold 101

E

- Eales disease 437
- ear pinna, chondritis 361
- EBUS *see* endobronchial ultrasound (EBUS)
- EBUS-TBNA 128, 129–130
  - lung cancer 129–130, 456–457
- echinacea 375
- echobronchoscope 208
  - TBNA with 208
- echocardiography
  - heart disease diagnosis 697
  - pulmonary hypertension 631
- e-cigarettes 259–260, 264, 775
- ecological fallacy 760
- ecological studies 759
- effect modifier 766–767
- efferocytosis 24
- EG-2 309
- EGFR (epidermal growth factor receptor) 464–465
- *EGFR* gene mutations 447
  - C797S with T790M mutation 448
  - exons 19 and 21 448, 465
  - lung cancer 447, 448–449, 464–465, 469, 470
  - T790M 448–449, 465, 466
- EGFR inhibitors 465
- eicosanoids, in exhaled breath condensate 191
- *EIF2AK4* gene mutations 630
- elastin, degradation, α_1-antitrypsin deficiency 744
- elderly
  - asthma *vs* COPD 314–315
  - dyspnoea 99
  - hospital-acquired pneumonia 384
  - lung abscess 280, 281
  - pleural infection 273, 277
  - pneumonia 377, 378
  - stage IV NSCLC 460
- electrocardiography (ECG) 109, 696–697
- electrocautery, airway obstruction 133
- electrolytes
  - disturbances, in cystic fibrosis 730
  - measurements, acid–base disorders 63, 66
- electromyography (EMG), diaphragm 655, 656, 657
- electronic cigarettes 259–260, 264, 775
- emboli
  - pulmonary *see* pulmonary embolism (PE)

  - tumoural 497
- embolic materials 648
- embolisation
  - pulmonary arteriovenous malformation 648
  - septic, infection spread 278
- embryology, respiratory system 6
- embryonal carcinoma 17
- emergencies *see* respiratory emergencies
- EMLA4 gene rearrangement 449
- emphysema 20, 324–331
  - aetiology 324
  - α_1-antitrypsin deficiency and 324–325, 744, 745
  - definition 325
  - diagnosis 326–327
  - *K*CO and *T*LCO 58
  - panlobular 745
  - quality of life 282
  - residual volume increase 282
  - severe, bronchoscopic therapy 131
  - total lung capacity 84
  - treatment
    - endoscopic 135–136
    - endoscopic lung volume reduction 283–284, 286
    - endoscopic valve placement 283–284
    - lung volume reduction surgery 95, 282
  - wasted ventilation, V'_E/V'_{CO_2} slope 73
  - *see also* chronic obstructive pulmonary disease (COPD)
- emphysema-like changes (ELCs) 669
  - in spontaneous pneumothorax 667
- empyema 274
  - investigations 276
    - chest radiography 275, 276
    - CT scan 276, 279
    - transthoracic ultrasound 165
  - management 277, 664
    - medical thoracoscopy/pleuroscopy 149
- enalapril 217
- end-expiratory lung volume (EELV) 48, 87
  - changes during exercise 73
    - in obese subjects 103
- end-inspiratory lung volume (EILV) 87
- endobronchial biopsy, blind, in sarcoidosis 362
- endobronchial coil insertion 136
- endobronchial drainage, lung abscess 280
- endobronchial lesions
  - central, sampling techniques 207–208
  - pulmonary carcinoid tumours 490
- endobronchial metastases 497
- endobronchial stents 130
- endobronchial tumours, bronchoscopic therapy 130–131
- endobronchial ultrasound (EBUS)
  - lung cancer 129–130, 456, 460
    - staging 460
  - radial 130, 134, 456
  - rare airway diseases 359
  - sarcoidosis 129, 130, 565
- endobronchial ultrasound-guided transbronchial fine needle aspiration (EBUS-TBNA) 128, 129–130
  - lung cancer 129–130, 456–457
- endobronchial valves (EBVs) 131, 135, 283
- endodermal sinus tumour 17
- end-of-life support
  - in cystic fibrosis 738
  - *see also* palliative care/treatment
- endoscopic lung volume reduction 282–287
  - blocking and nonblocking devices 283
  - bronchoscopic thermal vapour ablation 285
  - coil implantation 283, 284–285
    - complications 285
  - patient selection 285–286
  - polymeric lung volume reduction 285
  - techniques used in trials 285
  - valve placement 283–284
    - complications 284
- endoscopic treatment
  - airway obstruction 132–133
  - emphysema 135–136
  - peripheral malignancies 133–134
  - *see also* bronchoscopy; interventional pulmonology
- endoscopic ultrasound (EUS) 129–130
- endoscopy
  - bronchial, diagnostic *see* bronchoscopy
  - chest pain investigation 109
  - interventional *see* endoscopic treatment
  - malignant pleural mesothelioma 146
  - pleural adenocarcinoma 146
  - thoracoscopy *see* medical thoracoscopy/pleuroscopy (MT/P); thoracoscopy
- endothelial cell dysfunction
  - COPD 340
  - pulmonary hypertension 630
- endothelial cell loss, radiation-induced 612
- endothelin-1 (ET-1) 576, 704
  - inhibitors, idiopathic interstitial pneumonias 576–577
- endothelin receptor antagonist (ERA) 576–577
  - idiopathic interstitial pneumonias 577
  - pulmonary arterial hypertension 634
- endothoracic metastases 496
- End-TB strategy 426, 440
- endurance training 243
- energy imbalance 716, 731
- ENG (endoglin) gene mutations 646
- engraftment syndrome 714
- enterogenic cysts 515
- environmental assessment, hypersensitivity pneumonitis 559
- environmental exposures
  - exposome concept 765–768
  - hypersensitivity pneumonitis 557, 559, 560
  - lung cancer risk 453, 454
  - occupational asthma *see* occupational asthma
  - reduction, COPD management 328
  - sarcoidosis 563
- environmental tobacco smoke (ETS) 775, 776

- environment-wide association study (EWAS) 769
- EOLIA trial 302
- eosinophil(s)
  - in BAL fluid 13, 142
  - chronic rhinosinusitis and nasal polyps 306
  - eosinophilic exacerbations in COPD 333, 334, 336
  - granules 10
  - induced sputum 188
  - role 615
- eosinophil cationic protein 309
- eosinophilia
  - asthma 309
  - BAL 13, 142
  - bronchitis 111, 615–616
  - causes 616
  - chronic cough and 112
  - COPD 25, 322
  - eosinophilic granulomatosis with polyangiitis 638–639
  - hypereosinophilic syndrome 617–618
  - pulmonary infiltrates and (PIE) 606
  - secondary causes 617
  - sputum
    - asthma 188
    - chronic cough 188
- eosinophilic bronchitis 111, 615–616
- eosinophilic diseases 615–619
  - types, causes and associations 616, 617
- eosinophilic granulomatosis with polyangiitis (EGPA) 616, 637, 638–640
  - definition and criteria 638–639
  - epidemiology 637
  - investigations 638–640, 639–640
  - prognosis 642
  - relapsing/refractory, treatment 644
  - sites of involvement 639
  - treatment 642–644
- eosinophilic inflammation, chronic cough and 112
- eosinophilic pneumonia 616–617
  - drug-induced 599
- epidemiological studies 753–770
  - bias and errors 766–767
  - designs of studies 757–760
    - with aggregated data 759–760
    - with individual data 757–759
  - exposome concept *see* exposome concept
  - goals 754, 757
  - incidence and risk 755–756
  - measuring disease onset (incidence rate) 755–756
  - measuring effects of exposure to risk factors 757–760
    - experimental studies 757, 758, 759
    - observational studies 757, 758–759
  - measuring occurrence of health outcomes 754–755
    - prevalence 756–757
  - prevalence 756–757
  - quantitative assessment of exposure–health outcome relationship 760–763
    - contingency table 760
    - difference 760, 763, 764
    - ratio 760, 761–763
  - scales, measurements of outcomes/exposures 753–754
  - sensitivity and specificity 767–768
  - statistical association between exposure and health outcomes 763–765
    - causation 765
    - error types 763, 765
    - statistical methods used 769–770
- epidemiology, definition 754, 768
- epidermal growth factor receptor (EGFR) 464–465
  - gene mutations *see* EGFR gene mutations
- epiglottitis 374
- epithelial cells, ciliated 740, 741
- epithelial sodium channel (ENaC) 728
- epithelioid cell granuloma, noncaseating 565
- Epworth Sleepiness Scale (ESS) 523
- equal pressure point (EPP) 28, 33, 34
- ErbB family 448–449
- ergots, pleural injury 610
- erlotinib therapy 448, 465
  - lung cancer 465, 466
- errors 766
  - random 766
  - systematic 766
  - types, statistics 763, 765
- erythema nodosum 122
- erythromycin, in bronchiectasis 357
- *Escherichia coli*, aspiration pneumonia 412
- ESKAPE microbes 412
- etanercept therapy, idiopathic pulmonary fibrosis 577
- ethambutol
  - nontuberculous mycobacterial infections 445
  - pulmonary tuberculosis 421, 422
  - side-effects 422
  - tuberculosis in immunocompromised patients 430
    - HIV infection 686
- ethane 190
- ethionamide therapy, pulmonary tuberculosis 423
- etoposide, SCLC 468, 486
- eucapnic voluntary hyperventilation (EVH) tests 80–81
- European Respiratory Society (ERS)
  - antibiotics, for community-acquired pneumonia 381
  - bronchiectasis diagnostic testing 354–355
  - bronchiectasis treatment 356
  - chronic cough management 111
  - COPD patients for pulmonary rehabilitation 246
  - direct provocation/challenge test 78
  - dyspnoea, multidimensional nature 100
  - idiopathic interstitial pneumonia 574
  - malignant pleural effusion management 512, 513
  - noninvasive ventilation (NIV) 546
  - primary ciliary dyskinesia diagnosis 741, 742

  pulmonary arterial hypertension treatment 634, 635
  respiratory physiotherapy for bronchiectasis 232, 235
  spontaneous pneumothorax 157
  sputum, eosinophils in 188
  T_{LCO} and T_{LNO} 58
everolimus 492
  lymphangioleiomyomatosis 588
exendin-4 221
exercise
  asthma and 310
  bronchiectasis management 356
  in cystic fibrosis, benefits 235
  dyspnoea during 98, 100, 101
    see also dyspnoea, exertional
  neurophysiology of perceived dyspnoea during 98
  in obesity 720, 721
  see also physical activity
exercise challenge tests 80–81
exercise-induced bronchoconstriction (EIB) 80
exercise intolerance
  causes 70, 71
  COPD 70, 73, 74, 101, 245
  COPD and obesity 718
  interstitial lung disease 103
  variables/indices indicating 71–74
exercise testing *see* cardiopulmonary exercise testing (CPET)
exercise tolerance 70
  assessment, in pulmonary rehabilitation 245
  enhanced, by pulmonary rehabilitation 241
  improving, pulmonary rehabilitation 240
  predictor, of dyspnoea 97
exercise training
  COPD management 234, 240, 244–245
  dyspnoea, causing low adherence 99
  pulmonary hypertension 240
  in pulmonary rehabilitation 240, 242
    duration of programme 243
    individualised programmes 243
    maintaining effects 243
    see also pulmonary rehabilitation
  whole body 240
  see also pulmonary rehabilitation; respiratory physiotherapy
exertional dyspnoea *see* dyspnoea
exertional oscillatory ventilation (EOV) 74, 75
exhaled breath analysis 190–192
  asthma 191, 192
  biomarkers 190, 191, 192
  COPD 191, 192
  safety 190
  sample collection and analysis 190–191
  temperature 191
  validity 192
exhaled breath condensate (EBC) 190
exhaled breath temperature (EBT) 191
exhaled nitric oxide fraction (F_{ENO}) 190, 191, 192
  asthma 314
exogenous lipoid pneumonitis, drug-induced 599, 611
experimental epidemiological studies 757, 758
expiration 32, 33, 48, 83
  forced, vital capacity 86
  upper airway collapse in obstructive sleep apnoea 523, 524
expiratory flow limitation (EFL) 85, 86–87
expiratory muscles, testing 655
expiratory positive airway pressure (EPAP) 547
expiratory pressure, maximum (P_{Emax}) 84
expiratory reserve volume (ERV) 87
  decrease, in obesity 717
expiratory vital capacity (EVC) 86
exposome concept 765–768
  bias and errors 766–767
  sensitivity and specificity 767–768
extensively drug-resistant TB (XDR-TB) 201, 205, 418–419
  treatment 424–425
extracorporeal membrane oxygenation (ECMO), veno-venous 302
extragonadal germ-cell tumours (EGCTs) 516
  tumour markers 517–518
extra-oesophageal reflux disease 704
extrapulmonary tuberculosis (EPTB) 433–437
  diagnosis 433–434, 435
  in HIV infection 419, 686
  lymphadenitis 434
  prevalence 433
  risk factors 433, 434
  specific organ involvement 434–437
  treatment 434
  see also tuberculosis (TB)
extrinsic allergic alveolitis (EAA)
  BAL findings 143, 145
  diagnostic criteria 559

F

F2-isoprostanes, in exhaled breath condensate 191
factor H-related I (FHR I) deficiency 404
factor I 404
family history, asthma 308, 309, 313
farmer's lung 557, 558, 559, 560
fasudil 222
fatigue
  chemotherapy-induced 465
  in COPD 246
  of muscles 243
  palliative care 250–251
  of respiratory muscles 32
  in sarcoidosis 564
FDG (2-[^{18}F]-fluoro-2-deoxy-D-glucose) 182, 183
FDG PET *see* positron emission tomography (PET)
FDG PET/CT *see* positron emission tomography (PET)/CT
febrile neutropenia 707, 708

female reproductive tract, CF-related disease 737
*F*ENO (exhaled nitric oxide fraction) 190, 191, 192, 314
    analysers 190, 191
ferruginous bodies 10
FEV1 *see* forced expiratory volume in one second (FEV1)
FEV1/FVC ratio
    airway obstruction diagnosis 105
    α_1-antitrypsin deficiency 745
    asthma 312
    COPD 325
    lower limit of normal (LLN) 325
Feyrter cells 9
FGFR1 amplification 451
fibroblast dysregulation 574
fibroproliferative process, idiopathic interstitial pneumonias 569, 577
fibrosing mediastinitis 673–674
Fick equation 72
Fick's principle 28, 37
    diffusion impairment 35
ficolin 3 404
field walking tests 245
fine-needle aspiration biopsy 7
    transbronchial *see* transbronchial fine-needle aspiration (TBNA)
finger clubbing 120
F2-isoprostanes, in exhaled breath condensate 191
fissures, lungs 2
5As approach, smoking cessation 263, 264
FLAURA trial 448
Fleischner guidelines, pulmonary nodules 455, 501, 502, 503, 504, 505
flow cytometry 8
    lymphoproliferative tumours 16
fluconazole 407
fluorescence bronchoscopy 128–129
fluorescence *in situ* hybridisation (FISH) 450
fluorescence microscopy, TB diagnosis 420
2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) 182, 183
    FDG-PET *see* positron emission tomography (PET)
    FDG-PET/CT *see* positron emission tomography (PET)/CT
fluorochrome staining procedure 202
fluoroquinolones
    COPD exacerbations 335
    hospital-acquired pneumonia 386
    pulmonary tuberculosis 422
    resistance 419, 420
fluoroscopy
    chest 159
    sampling of peripheral pulmonary lesions 208
fluticasone propionate, side-effects 349
focal lung disease, HRCT 179
folliculin (FLCN) gene 586
forced expiratory ratio (FER) 86
forced expiratory volume in one second (FEV1) 83, 87
    age and 88
    α_1-antitrypsin deficiency 745
    asthma 312
    bronchial provocation testing 77, 79
        direct tests 77, 79
        indirect tests 80, 81
    COPD 258
        diagnosis of 325–326
        exacerbation diagnosis 334
        heart failure and 694
    decline
        lung transplantation problem 291
        lymphangioleiomyomatosis 587
        rate, COPD 327, 328
    lung cancer 460–461
    lung transplantation in cystic fibrosis 738
    post-operative values (ppoFEV1), lung resection 94, 95
    reduced, in obesity 717
    sputum induction and 188
forced oscillation technique (FOT) 51
forced vital capacity (FVC) 83, 86
    age and 88
    idiopathic pulmonary fibrosis 554
    reduced, in obesity 717
forceps biopsy 207
foreign body, removal 131
formoterol 317, 345
fossil fuel combustion 772
Fowler technique 55
fractional exhaled nitric oxide measurement *see* *F*ENO (exhaled nitric oxide fraction)
fractures, radiation-induced 488
FRC *see* functional residual capacity (FRC)
functional residual capacity (FRC) 30, 48, 83, 84
    decreased
        obesity 717, 718
        restrictive respiratory diseases 87
    definition 86
    increase, obstructive pulmonary diseases 86–87
    measurement 87–88
fungal infections
    in cystic fibrosis 733, 734
    cytological changes 12
    in haematological disease 708
    immunocompromised hosts 389
        HIV-infected patients 684–685
        humoral immune deficiency 379, 676
        neutropenia 391, 404
        pneumonia 389, 391
        primary immunodeficiency 676
    lung abscess due to 279
    post-transplant 407
    see also specific fungal infections
'funnel chest' *see* pectus excavatum (PE)
furosemide, respiratory sensation modulation 106
Fusarium, pneumonia due to 391
FVC *see* forced vital capacity (FVC)

G

gabapentin, in chronic cough 112
galactomannan antigen test 391
gallium-67 citrate 182
gallium-67 scintigraphy, inflammatory diseases 182–183
gallium-68 182, 183
  PET-CT with, pulmonary carcinoids 492
ganciclovir 407
gas dilution techniques 88
gas embolism, arterial 783
gas exchange *see* pulmonary gas exchange
gas transfer 54–59
gas transfer factor *see* transfer factor of the lung for carbon monoxide (T_{LCO})
gastric acid
  aspiration 411, 701
    airway/lung damage 411–412, 413
  microaspiration 411, 578
gastric disease, in cystic fibrosis 736
gastrointestinal disease
  in cystic fibrosis 731, 736
  lung disease with 701–706
  pulmonary symptoms, and causes 701, 702
  tuberculosis 436
gastrointestinal stromal tumour 18
gastrointestinal tract, barotrauma effect 783
gastro-oesophageal reflux (GOR) 374, 411
  'silent reflux' 412
  symptoms 412
  therapeutic approaches 413
  see also aspiration
gastro-oesophageal reflux disease (GORD) 701, 704
  chronic cough and 111, 112
  clinical features 701, 704
  comorbidities
    asthma 315, 414
    bronchiectasis 413
    COPD 414
    cystic fibrosis 414
    post-transplant obliterative bronchiolitis 413
    pulmonary fibrosis 414
  detection/diagnosis 412, 701, 704
  management 413, 414
  prevalence 413
  risk factors 704
  treatment 578, 704
gefapixant 112
gefitinib therapy 448, 465, 466
gemcitabine therapy, lung cancer 466
  NSCLC 469
gene mutations
  'driver' 447, 464
  idiopathic interstitial pneumonias 569
  lung cancer *see* lung cancer
  primary ciliary dyskinesia 740, 742
  tuberous sclerosis complex 585
  see also specific genes
gene sequencing
  in cystic fibrosis 731
  Mycobacterium tuberculosis complex 205
genetics *see* specific diseases
Geneva score 620, 621, 622
GeneXpert system 205
genitourinary tuberculosis 436
genomic testing, multiplex, lung cancer 447–448
genotoxic carcinogens 453, 454
genotyping, *Mycobacterium tuberculosis* complex 205
geographic information systems (GIS) 759–760
germ cell tumours
  cytology 17
  germinomatous 515, 519
  mediastinum involvement 515, 516
giant cell(s) 9, 12
  multinucleated 641
giant cell pneumonitis 13
GINA *see* Global Initiative for Asthma
glitazones 220
Global Burden of Diseases Study 2015 772
Global Initiative for Asthma (GINA) 188, 225, 414
  asthma management 316, 317, 318
Global Initiative for Chronic Obstructive Lung Disease (GOLD) 244, 245, 324, 348
  COPD classification 326, 328–329
global warming 772
glucagon-like polypeptide 1 (GLP1) 220, 221
glucagon-like polypeptide 1 receptor (GLP1R) agonists 220–221
glucocorticosteroids
  Pneumocystis jirovecii pneumonia 684–685
  pulmonary vasculitis 643
  topical/nasal, in chronic rhinosinusitis 307
  see also corticosteroid therapy
glucose 6-phosphate dehydrogenase deficiency 684
glutathione (GSH) 576
goblet cells 9
Goodpasture's disease 638
GORD *see* gastro-oesophageal reflux disease (GORD)
graft *versus* host disease (GVHD) 709, 714
grain handler's lung 560
Gram stain 7, 8
  sputum 196
granulocyte macrophage–colony stimulating factor (GM-CSF)
  autoantibodies 589, 590
  disruption in pulmonary alveolar proteinosis 589
  pulmonary alveolar proteinosis treatment 591
granuloma(s)
  adult pulmonary Langerhans cell histiocytosis 582
  noncaseating epithelioid cell 565
  pulmonary tuberculosis 418
  sarcoid, cytological findings 12–13
  sarcoid-like 17
granulomatosis with polyangiitis (GPA) 362, 374, 637, 640, 641
  epidemiology 637
  investigations 640, 641
  pathogenesis 637–638
  prognosis 642

  - treatment 642–644
  - *see also* pulmonary vasculitis
- granulomatous disorders 581, 582
- granulomatous-lymphocytic interstitial lung disease (GLILD) 677, 678
  - treatment 679
- granulomatous reactions, cytological detection 11
- granzyme B 23
- gravity 38
- Grocott's methenamine silver stain 12
- ground-glass nodules (GGN), pure *see* ground-glass opacities (GGOs)
- ground-glass opacities (GGOs) 455–456, 501, 502
  - clinical course (pure GGNs) 455–456
  - drug-induced respiratory disease 601
  - eosinophilic granulomatosis with polyangiitis 639, 640
  - idiopathic pulmonary fibrosis 573
  - management 504
  - nonspecific interstitial pneumonia 572, 678
  - pulmonary alveolar proteinosis 590
  - pulmonary arteriovenous malformations 647
  - systemic sclerosis 724
- group A streptococcal infections 373, 375
- growth hormone-releasing hormone (GHRH) 491
- guanylate cyclase inhibitor 634
- gynaecomastia 122

H

- haemagglutinin (H) 393
- haematological diseases 707–715
  - drug-related pulmonary complications 710
  - noninfectious pulmonary complications 710–714
    - late-onset 714
  - pulmonary complication vulnerability 707
  - pulmonary infections 707–710
    - bacterial infections 707–708
    - endogenous source 708
    - exogenous source 708, 709
    - fungal infections 708
    - viral infections 708
- haematopoietic stem cell transplantation (HSCT)
  - allogeneic
    - immunodeficiency after 389, 709
    - lung function tests after 714
    - noninfectious pulmonary complications 710, 714
    - opportunistic infections after 389, 405, 708–709
    - autologous, infections/respiratory events after 708
  - CMV infections/pneumonia 390
  - GVHD 709
  - idiopathic interstitial pneumonias 579
  - immunosuppression after 388, 389
  - nontuberculous mycobacterial infection 444
  - opportunistic infections after 389, 405, 708–709
  - phases after, and infections associated 709, 710
- haematoxylin–eosin stain 7
- haemolytic anaemia, pulmonary infections 709
- haemophagocytic lymphohistiocytosis 402
- *Haemophilus* (spp.), in HIV infection 408, 683
- *Haemophilus influenzae* infection
  - aspiration pneumonia 412
  - bronchiectasis 355
  - COPD exacerbation 334
  - diagnostic approach 195
  - in HIV infection 683
  - hospital-acquired pneumonia 384
  - pneumonia complicating influenza 394
  - primary ciliary dyskinesia 743
  - primary immunodeficiency 675, 676
  - type B (Hib), epiglottitis due to 374
- haemoptysis 115, 293
  - acute respiratory failure with 297
  - conditions causing 115
  - in cystic fibrosis 734
  - life-threatening 115
  - management 115, 298
  - pulmonary tuberculosis 419
  - recurrent 115
  - severe 297–298
    - acute respiratory failure 294, 296, 297–298
  - volume 298
- haemorrhage
  - alveolar *see* alveolar haemorrhage
  - pulmonary, in haematological disease 710, 711
  - risk, in pulmonary arteriovenous malformations 647
- haemothorax 663
- 'halo' sign 391
- hamartomas, pulmonary 493
- Hamman's sign 670
- head and neck carcinoma 496, 497
- health
  - inequalities, smoking and 259
  - outcome, measurement 754–755
    - *see also* epidemiological studies
- healthcare-associated pneumonia (HCAP) 383
  - *see also* hospital-acquired pneumonia (HAP)
- healthcare resources, decrease in use by pulmonary rehabilitation 242
- hearing impairment 743
- heartburn 701, 702
- heart disease *see* cardiac disease; cardiovascular disease
- heart failure
  - adaptive servoventilation and 267
  - airflow obstruction in 695
  - central sleep apnoea 530, 531
  - Cheyne–Stokes respiration 530, 531
  - congestive *see* congestive heart failure (CHF)
  - in COPD 218, 692–693, 694
  - lung disease diagnosis requirements 696–698
  - pleural effusion 660
  - respiratory symptoms 695
  - treatment, effects on lungs 698
- heart rate, peak ($\mathrm{HR}_{\mathrm{peak}}$) 72
- heart rate reserve (HRR) 72

Heaviness of Smoking index 263
Heerfordt syndrome 565
helium 55, 56
helium dilution method 88
helminthic infections 616
Henderson–Hasselbalch equation 29, 63
hepatobiliary disease, in cystic fibrosis 730
hepatopulmonary syndrome (HPS) 701, 702, 704–705
  clinical features 704, 705
  diagnosis 705
  pathogenesis 704
HER2 (ErbB2) 448
  gene mutations 449
HER3 (ErbB3) 448
HER4 (ErbB4) 448
  gene mutations 449
herd effect/immunity 375
Herder's model 455, 503
hereditary haemorrhagic telangiectasia (HHT) 646
  aetiology and mutations 646
  Curaçao diagnostic criteria 646, 647
heritable pulmonary arterial hypertension 629
herpes simplex infections, cytological changes 11, 12
herpes simplex pneumonitis 11, 12
high altitude, physiological response 36, 779–780
high-altitude cerebral oedema (HACE) 780, 781
high-altitude periodic breathing 534, 779, 780
high-altitude pulmonary hypertension (HAPH) 782
high-altitude pulmonary oedema (HAPE) 781–782
high altitude-related disease 779–782
  illnesses 780–782
  in patients with lung disease 782
  physiological responses to altitude 36, 779–780
  pressure changes 779
  prevention/management 782
high-flow nasal cannula (HFNC) oxygen therapy 255–256
  noninvasive ventilation *vs* 256, 551
high-intensity behavioural interventions, smoking cessation 262, 263
high-resolution computed tomography (HRCT) 170, 175–180
  diseases presenting with specific patterns 177
  expiratory 175
  indications 175, 176, 177
  scanning patterns 571
  in specific diseases
   adult pulmonary Langerhans cell histiocytosis 582, 583
   Aspergillus pneumonia 391
   bronchiectasis 354
   constrictive bronchiolitis 176
   diffuse interstitial lung disease 175, 176–178
   diffuse interstitial lung disease, monitoring 178–179
   drug-induced respiratory disease 599, 601–602, 603
   eosinophilic granulomatosis with polyangiitis 639–640
   eosinophilic pneumonia 617
   focal lung disease 179
   hypersensitivity pneumonitis 559
   idiopathic interstitial pneumonias 570, 571
   idiopathic pulmonary fibrosis 176, 555
   interstitial lung disease 724
   lymphangioleiomyomatosis 586
   pneumonia in immunocompromised hosts 390, 391
   pulmonary alveolar proteinosis 590
   pulmonary disease in primary immunodeficiency 678
   pulmonary hypertension 633
   sarcoidosis 565, 566
  technique 175
  usual interstitial pneumonia (UIP) pattern 554, 555, 571
high-speed video microscopy analysis (HSVMA) 741–742
hila, anatomy 4
hilar amyloid lymphadenopathy 594
hilar lymph nodes
  drug-induced lymphadenopathy 603
  metastatic tumours 498
hilar-mediastinal region lesions, sampling techniques 209
histamine bronchial provocation testing 77, 78
histiocytes 11
histology
  asthma 309
  COPD 309
  HRCT relationship, diffuse interstitial lung disease 177
  lung 301
  pulmonary hypertension 630
histone deacetylase (HDAC)2 347, 348
histospecific imaging patterns 599, 607
HIV infection
  epidemiology 681
  immunosuppression 388, 389, 400
  people living with (PLHIV) 681, 682, 683, 687, 688, 689
   smokers, diseases associated 688, 689
  TB co-infection *see* tuberculosis (TB)
HIV-related disease 681–691
  aetiology 682
  antiretroviral therapy-associated symptoms 689–690
  infections 388, 389, 390, 408, 429, 682–688
   bacterial 682–683
   fungal 684–685
   nontuberculous mycobacterial (NTM) 443, 686
   Pneumocystis jirovecii pneumonia 390, 408, 684–685
   tuberculosis *see* tuberculosis (TB)
   viral 683
  malignant conditions 688
  nonmalignant, noninfectious conditions 688–690
   COPD 688–689
   pneumonitis 689

        pneumothorax 689
        pulmonary arterial hypertension 689
    respiratory pathogens in 408, 682, 683
HLA genes, sarcoidosis and 563
HMB-45 585
Hodgkin cells 16
Hodgkin disease 516, 584
honeycombing 570, 724
horizontal fissure 2
hospital, lung cancer surgery volume 474, 475
hospital-acquired pleural infection 274, 275
hospital-acquired pneumonia (HAP) 378, 383–387
    classification 383
    definition 383
    diagnosis 385–386
        algorithm 385
    epidemiology 383–384
    management 380–381
    microbiology 384–385
    mortality 385, 386, 387
    pathogenesis 384
    risk factors 383–384, 385
    time of onset 385
    treatment 386–387
        guidelines 386
host defence systems 20–27
    immunocompromised *see* immunocompromised hosts
    see also immune response
HOT-HMV trial 270
hot tub lung 560
household air pollution (HAP) 775
HRCT *see* high-resolution computed tomography (HRCT)
HSCT *see* haematopoietic stem cell transplantation (HSCT)
Hull Airways Reflux Questionnaire 111, 113
human epidermal growth factor receptor (HER)1 448
human herpes virus-8 688
humidification 267
humidifier lung 560
humoral immune deficiency 404
    community-acquired pneumonia in 377, 379
    infections associated 675, 676
humoral immune response 404
hydrofluorocarbon (HFC) 210
hydrogen peroxide, in exhaled breath condensate 191
5-hydroxyindoleacetic acid 492
hyperaldosteronism, primary 67
hyperbaric oxygen therapy 673, 785
hypercalcaemia, lung cancer 456
hypercapnia 34, 42
    acute, causes 542, 543
    arterial pH 63
    in asthma 313
    chronic, end-stage interstitial lung disease 271
    chronic daytime 536
    diurnal, in obesity 719
    obesity hypoventilation syndrome 537
    sleep-related hypoventilation syndromes 536, 537
hypercapnic respiratory failure 62, 542, 543
    arterial blood gas analysis 61, 62
    causes 543–544, 653
    NIV *see* noninvasive ventilation (NIV)
    oxygen therapy 253
hyperchloraemic acidosis 64, 65
hypercontractility, oesophagus 703
hypereosinophilic syndrome (HES) 616, 617–618
    idiopathic 618
    pulmonary 618
    variants 618
hyper IgE syndrome 402
hyper IgM syndrome 401
hyper-inflammatory state, in cystic fibrosis 733
hyperinflation (lung) 87, 310
    asthma, exertional dyspnoea 104
    COPD 718
    dynamic 73
    obese individuals, in exercise 103
    static 282
hyperkeratosis 10
hyperleukocytosis 711
hyperoxia 253
hyperoxic rebreathing test 42, 43
hypersensitivity
    drug-induced 598
        abacavir 690
    to environmental stimuli 557
        chronic cough and 111
hypersensitivity pneumonitis (HP) 443–444, 557–562, 751
    antigens causing 559, 560
    chronic 559
        HRCT 559
        idiopathic pulmonary fibrosis *vs* 561
        treatment 561
    diagnosis 555, 559–560
    diagnostic criteria 559
    differential diagnosis 561
    environmental assessment 559
    epidemiology 557–558
    host factors 558
    occupational 557–558, 559, 560
    pathological mechanism 558
    prognosis 561
    risk factors 558
    summer-type 557, 560
    symptoms/findings 558–559
    treatment 560–561
    types 560
hypertension, pulmonary *see* pulmonary hypertension (PH)
hypertonic saline
    bronchial provocation testing 81–82
    nebulised, in primary ciliary dyskinesia 742
hyperventilation 29, 529, 530
    chemoreceptor-mediated, high altitude 779

hyperventilation syndrome, respiratory physiotherapy 234
hypocapnia 62, 63
hypochloraemia 67
hypogammaglobulinaemia 515
hypoglycaemic drugs, impact on lung 220–222
hypokalaemia 67
hyponatraemia 67
hypopnoea, obstructive *see* obstructive sleep apnoea–hypopnoea syndrome (OSAHS)
hypothesis tests 763
hypoventilation
  alveolar 34–35, 38
    arterial hypoxaemia due to 34–35, 61, 62
  genetic syndromes associated 269
  hypoxaemia with 542
  nocturnal 535–536, 657
  during REM sleep 268
  respiratory failure 542
hypoventilation syndromes 535–540
  aetiology 535–536, 537–539
    extra-/intrapulmonary restrictive disorders 535, 536, 537–538
    obstructive disorders 535, 536, 539
  clinical features 536
  diagnosis 536
  management 538, 539
  pathophysiology 535–536
  sleep-related 268, 523
hypovolaemia 66, 67
hypoxaemia 29, 34
  acute, oxygen therapy 253, 256
  acute exacerbation of COPD 544
  aetiology 28, 34–39, 61, 62
    alveolar hypoventilation 34–35, 61, 62
    diffusion impairment 35–36, 62
    reduced RQ 34
    right-to-left shunt 37, 61, 62
    ventilation–perfusion mismatch 38–39, 62
  arterial blood gas analysis 61, 542
  chronic 254
    long-term oxygen therapy 254, 255
  high altitude 780, 782
  with hypoventilation 542
  in idiopathic interstitial pneumonias 570
  mechanisms 542
  nocturnal, obesity hypoventilation syndrome 537
  oxygen therapy 36, 61, 253
    effect 36, 61
    see also oxygen therapy
  respiratory failure *see* hypoxaemic respiratory failure
  ventilatory response during sleep 536
hypoxaemic respiratory failure 62, 541, 542
  arterial blood gas analysis 61, 62, 542
  causes 542, 549
  management 542
    noninvasive ventilation 549–550
  pathophysiology 542
hypoxia
  hepatopulmonary syndrome 704–705
  hypobaric 534
  obstructive sleep apnoea 524
  pulmonary hypertension due to 629, 630
  ventilatory response 41, 42
    estimation 44–46
hypoxia-withdrawal test (Dejours) 41, 45–46
hypoxic ventilatory decline 44
hysteresis 85

I

IASIS Trial 387
iatrogenic cardiac injury 597
iatrogenic pericardial effusion 603
iatrogenic pulmonary hypertension 610
iatrogenic pulmonary vein stenosis 603
iatrogenic respiratory disease (IRD) 595–611
  causes 596, 597
  diagnostic workup 596
    imaging 603
  epidemiology 599
  life threatening 596
  pathophysiology 597–599
  see also drug-induced respiratory disease (DIRD)
ibrutinib 708
iclaprim 387
idelalisib 713
idiopathic central sleep apnoea 529, 533
idiopathic hypereosinophilic syndrome 618
idiopathic interstitial pneumonias (IIPs) 568–580
  acute exacerbation 573
    biopsy/diagnosis 573
  acute interstitial pneumonia 297
  after haematopoietic stem cell transplantation 579
  classification 568, 569
  clinical features 570
  conditions included 569
  diagnosis 570–572
    HRCT 570, 571
    lung biopsy 572, 573
  end-of-life care 579
  epidemiology 568–569
  familial 569
  gene mutations 569
  major 569
  natural history and exacerbations 572–573
  oxidant agent production 576
  pathogenesis 568, 569, 574, 577
    fibroblast dysregulation 574
  physiology 570
  pulmonary embolism in 577
  rare 569
  treatment 574–578
    anti-inflammatory drugs 574–575
    lung transplantation 288, 290, 578–579
    novel strategies 575–578
    oxygen 578
    stem cell-based therapy 579

  see also desquamative interstitial pneumonia (DIP); idiopathic pulmonary fibrosis (IPF)
idiopathic pneumonia syndrome (IPS) 714
idiopathic pulmonary arterial hypertension 628, 631
  K_{CO} and T_{LCO} 58
idiopathic pulmonary fibrosis (IPF) 553–556
  acute exacerbations, criteria 556, 573
  chronic hypersensitivity pneumonitis vs 561
  clinical features 554
  diagnosis 554–555
    algorithm 572
    BAL fluid findings 145
    HRCT 176, 177, 554, 555, 570
  end-of-life care 579
  epidemiology 553–554
  familial variants 569
  gastro-oesophageal reflux and 414, 578
  genetic factors 554, 569
  natural history 573
  pathophysiology 554, 579
  prognosis 553, 556, 573, 576
  pulmonary hypertension in 693
  risk factors 554
  treatment 555–556, 574
    guidelines 556, 574, 576
    lung transplantation 288, 290
    nonpharmacological 555
    pharmacological 555, 556, 575, 577
  see also idiopathic interstitial pneumonias (IIPs)
idiopathic subglottic stenosis 361
IgA, IgE, IgG, IgM *see entries beginning* immunoglobulin
IGRAs *see* interferon-γ release assays (IGRAs)
ILD *see* interstitial lung disease (ILD)
image-guided percutaneous drainage, lung abscess 280
imatinib therapy 577
immersion pulmonary oedema 785
immune checkpoint(s) 451
immune checkpoint inhibitors (ICIs) 227–230, 451
  adverse events 598
  lung cancer 464, 467–468
    NSCLC 464, 467–468, 469
  predictive marker of benefit from 230
  respiratory disease due to 596
  side-effects 228, 467, 598
  see also CTLA4 pathway; PD-1; PD-L1
immune evasion 227, 451
immune reconstitution disease (IRD) 443
  antiretroviral drug therapy and 443, 687, 689–690
  intracranial 687
  paradoxical type 689
immune reconstitution inflammatory syndrome (IRIS) 430
immune response 227
  adaptive/acquired 20, 21–25
    dysfunction, pneumonia predisposition 377
  to allergens 223
  dysfunction, pneumonia predisposition 377
  hypersensitivity pneumonitis 558
  to infections 676
  innate 20, 21–25
    in COPD 21
  in lung 301
  pulmonary tuberculosis 417–418, 419, 429
  Th1/Tc1 response in COPD 21
  tumour cell elimination 451
  tumour cell escape phase 451
immune surveillance defect 677
immune tolerance 224
  by tumour cells 467
immunisation *see* vaccination
immunochromatographic test (ICT) 197
immunocompromised hosts, opportunistic infections 388, 400–410
  acquired immunodeficiency types 388, 389, 400, 404–409
    asplenia 409
    bone marrow/stem-cell transplantation 390, 405
    HIV infection 388, 389, 390, 408, 429
    iatrogenic 389, 429
    neutropenia 389, 391, 405
    solid-organ transplantation 389, 400, 405–408, 429
  diagnosis of infections 389
  in HIV infection 388, 389, 390, 408, 429, 682–688
    see also HIV-related disease
  infection types
    Aspergillus pneumonia 391, 405, 407
    Candida pneumonia 405, 407
    CMV pneumonia 390, 406–407
    in HIV infection 682–688
    Pneumocystis jirovecii pneumonia 390, 408, 684
    pulmonary infections 389, 405–408
    tuberculosis 390, 408
    see also specific pathogens
  nontuberculous mycobacteria 443
  pneumonia *see* pneumonia
  in primary immunodeficiency 400–404
    see also primary immunodeficiency disorders (PID)
immunocytochemistry
  adenocarcinoma of lung 14
  benign non-neoplastic disorders of lung 14
  germ cell tumours 17
  lymphoproliferative/myeloid disorders 16–17
  squamous cell carcinoma 14
  see also immunohistochemistry
immunodeficiency 400
  acquired 390, 400, 404–409
  innate 403
    see also phagocytes, professional
  opportunistic infections in *see* immunocompromised hosts, opportunistic infections

  primary *see* primary immunodeficiency disorders (PID)
  pulmonary infections 400
  tuberculosis risk 429, 430
  uraemia-associated syndromes 429–430
immunoediting 451
immunoglobulin A (IgA)
  in respiratory infections 676
  secretory 676
immunoglobulin E (IgE)
  allergen immunotherapy 224
  allergic reaction 223
  chronic rhinosinusitis 306
  measurement, asthma 313
  monoclonal antibodies to 350
  total IgE 313
immunoglobulin G (IgG)
  hypersensitivity pneumonitis 558
  IgG1 monoclonal antibody *see* mepolizumab
  IgG4, allergen-specific 224
  in respiratory infections 676
immunoglobulin M (IgM), tests for respiratory infections 198
immunohistochemistry
  COPD 22
  mesothelioma 511
  pleural metastases 511
  see also immunocytochemistry
immunology 20–27
immunomodulatory agents, sarcoidosis 567
immunosuppressants (immunosuppressive drugs)
  asthma 351
  connective tissue disease with ILD 725
  inflammatory bowel disease 705
  lung transplantation 291
  new 408
  sarcoidosis 567
immunosuppression
  causes/conditions
    HIV infection 388, 389, 400
    iatrogenic 388, 389, 429
    neutropenic 388, 389, 405
    pneumonia association 388
    solid-organ transplant recipients 388, 389, 400
    types 388
      infectious complications 388, 389
  ‘net state’ of 388
  see also immunocompromised hosts, opportunistic infections
immunotherapy
  allergen-specific *see* allergen immunotherapy (AIT)
  asthma 318
  lung cancer *see* lung cancer treatment
  malignant pleural mesothelioma 512
incidence 755–756
  prevalence relationship 756
incidence proportion 755
incidence rate 755–756
incremental exercise testing 70–71, 74, 245
indacaterol 345
indoor pollution 775–776
induced sputum *see* sputum, induced/induction
indwelling pleural catheter (IPC) 513
  pleural effusion management 664
  pleural infection associated 278
inertance 30
infantile larynx (laryngomalacia) 366–367
infections *see* respiratory infections
infertility 730, 737, 743
infiltrative disease, acute respiratory failure 294, 296, 297
inflammasone 21, 26
inflammasone inhibitory molecules 21
inflammation 20
  AT1R blockers reducing 216
  ACE inhibitors reducing 216
  airway *see* airway inflammation
  ARDS pathophysiology 300, 301
  aspiration of gastric acid and 411
  bronchial disorders 11
  cells *see* inflammatory cells
  chronic
    asthma 308
    COPD 20, 322, 339, 340, 341
    pathogenesis/cell types 21, 22, 23, 24, 25, 341, 693–694
  chronic rhinosinusitis 306
  COPD 20, 322, 339, 340, 341
    see also chronic obstructive pulmonary disease (COPD)
  local, smoking triggering 340
  in lung and heart, process 693–694
  mediators *see* inflammatory mediators
  radiotherapy-induced 612
  regulation, by cytokines in COPD 21, 22, 26
  statins effect 217, 218
  systemic
    COPD 340, 341, 693
    COPD and ischaemic heart disease 693–694
    diseases with 340, 693
    low-grade, in asthma and COPD 215
    obesity-related 718
    pathogenesis 693–694
    smoking triggering 340, 693
  type-1 322
  type-2 306, 307, 322
    asthma 322
inflammatory bowel disease (IBD)
  immunosuppression and 705
  tracheobronchial/pulmonary lesions in 701–702, 705
inflammatory bronchial disorders, chronic 11
  see also asthma; bronchiectasis
inflammatory cells 9, 20–21
  COPD 20–21, 322, 325
  HMG-CoA reductase action 217, 218
  idiopathic interstitial pneumonias 569
  pulmonary infections 11
  radiation-induced injury 612

inflammatory diseases (lung)
  diagnosis, gallium-67 scintigraphy 182–183
  hypersensitivity pneumonitis *see* hypersensitivity pneumonitis (HP)
  of lung interstitium *see* idiopathic interstitial pneumonias (IIPs)
  see also inflammation; specific diseases
inflammatory–fibrotic process 569, 577
inflammatory mediators
  air pollutants inducing 777
  ARDS pathophysiology 301
  asthma 322
  chronic airway inflammation 322
  COPD 340
  hypersensitivity pneumonitis 558
  idiopathic interstitial pneumonias 569
  in sputum 188
influenza 374, 379, 393–399
  avian influenza virus outbreaks 397
  chemoprophylaxis 395–396
  clinical features 394
  complications 394–395
  diagnosis 395
    practice points 399
  epidemiology 394
  incubation period 394
  pandemic 393, 396, 397
    mortality 396, 397
    noninvasive ventilation 550
  pneumonia complication 379, 394
  seasonal 393, 394
  transmission 394
  treatment 375, 395
  vaccination 375, 381, 395–396
    COPD 328, 336
    lymphangioleiomyomatosis 588
    trivalent and quadrivalent vaccines 396
  virology 393
influenza A, in HIV infection 683
influenza A viruses 393, 394, 396
influenza B viruses 394
influenza-like illness, community setting 399
influenza viruses 26, 393
  avian 397
  neuraminidase inhibitor resistance 396
  rapid method for detection 197
  subtypes 393, 394, 396
information bias 766
inhalation fever 561
inhaled corticosteroids (ICS) 348
  asthma management 308, 317, 345, 348
  bronchiectasis treatment 356
  COPD exacerbation prevention 337, 348
  COPD management 329, 345
  eosinophilic bronchitis 615–616
  side-effects 349
  see also corticosteroid therapy
inhaled drug therapy 210–214
  physiotherapists' help 233
inhalers
  breath-actuated pMDIs 212, 213
  characteristics of types 212–213
  correct use 211, 213
  dry powder (DPIs) 212, 213
  misuse/errors in use 210, 214
  nebulisers 212, 214
  pressurised metered-dose (pMDIs) 210, 211, 212
  reviewing technique with patient 214
  selection of correct type 213, 214
  soft-mist (SMI) 211, 213–214
  types 210–213
innate immune response 20, 21–25
innate immunodeficiency 403
  see also phagocytes, professional
innate lymphoid cells (ILC) 23–24
  type-1 (ILC1) 23
insect venom, allergy 224
inspiration 31–32, 33, 48, 83
  airway resistance measurement 50
  inspiratory vital capacity 86
  oxygen transport 35
  unsatisfied, in COPD 101
inspiratory capacity (IC) 87
  decreased
    asthma 104
    COPD 101
    hyperinflation 87
  increased in obesity 717
inspiratory–expiratory radiography 157
inspiratory muscle(s)
  measurement 655
  training, in COPD 234
  weakness
    K_{CO} and T_{LCO} 58, 655
    neuromuscular diseases 539, 655, 657
    sleep disordered breathing 657
inspiratory-muscle pressure (P_{mus}) 29–30, 48, 49
inspiratory positive airway pressure (IPAP) 547
inspiratory pressure, maximum (P_{Imax}) 84, 100
  decrease in COPD 101
inspiratory reserve volume (IRV) 87, 101
  interstitial lung disease 102
inspiratory vital capacity (IVC) 86
insulin resistance (IR) 525
intensity-modulated radiotherapy (IMRT), NSCLC 482, 483
intensive care unit, respiratory physiotherapy in 238
interferon-γ (IFN-γ)
  in COPD 21
  deficiency, idiopathic interstitial pneumonias 569
  pulmonary tuberculosis pathogenesis 417
  therapeutic, idiopathic interstitial pneumonias 575–576
interferon-γ release assays (IGRAs) 421, 431
  extrapulmonary tuberculosis 434, 436
  latent TB detection 439
  TB detection in immunocompromised hosts 431
interleukin-1 (IL-1), receptor antagonist 569
interleukin-1β (IL-1β) 26
interleukin-5 (IL-5) 306, 618

    antibodies to 350
interleukin-6 (IL-6) 340
interleukin-7 (IL-7) 21
interleukin-8 (IL-8) 414
interleukin-15 (IL-15) 417
interleukin-17A (IL-17A) and IL-17F 21
interleukin-18 (IL-18) 26
interleukin-21 (IL-21) 22
interleukin-22 (IL-22) 21, 24
interleukin-27 (IL-27) 21
interleukin-33 (IL-33) 306
International Standards of Tuberculosis Care (ISTC) 426
interstitial lung disease (ILD) 553, 568
    characteristics 553
    in connective tissue diseases 723, 724, 725
    diagnosis
        bronchoalveolar lavage 138, 141, 143, 145
        in connective tissue diseases 724
        gallium-67 scintigraphy 182
        gallium-68 scintigraphy 183
        HRCT 724
        lung biopsy 724
    diffuse *see* diffuse interstitial lung disease (DILD)
    diving and 785
    drug-induced 599, 604, 606
    dyspnoea 102–103
    exercise intolerance 70
    exercise testing 72
        as prognostic indicator 75
    histopathological classification 723
    management
        in connective tissue diseases 725
        long-term ventilation 271
        lung transplantation 288
        respiratory physiotherapy 235–236
    oxygen pulse, exercise testing 72
    in primary antibody deficiency 677
    pulmonary gas exchange impairment 75
    smoking and 13, 259
    see also specific diseases
interval scale 753, 754
interventional pulmonology 132–137
    applications and future development 132–136
        central airway obstruction 132–133
        complex pleural effusions 134–135
        emphysema 135–136
        peripheral malignancies 133–134
    benefits/importance 132, 136
    indications 132
    techniques used 136
intervention studies 758
intrabronchial valves (IBVs) 283
intraoperative interventions, to reduce complications 93
intrapleural pressure (PIP) 28, 30, 31, 33, 48, 84
    measurement 51
intrapulmonary shunt, ARDS pathophysiology 300, 301
intrathoracic pressure, negative, obstructive apnoea 524
IPF *see* idiopathic pulmonary fibrosis (IPF)
ipilimumab 228, 229, 468
ipratropium bromide 346
irritant-induced asthma (IIA) 748, 749, 750
isavuconazole 391
ischaemic heart disease (IHD)
    COPD and 692, 693–694
        exacerbations 333
        risk factors and inflammatory response 693–694
    diagnosis 695, 697
    respiratory symptoms 695
    treatment, effects on lungs 698
isocapnic hypoxia 44
isoniazid
    latent tuberculosis 426, 439
    nontuberculous mycobacterial infections 445
    pulmonary tuberculosis 421, 422
    resistance to, detection 205
    side-effects 422, 426
    tuberculosis in immunocompromised hosts 430
        HIV infection 686
8-isoprostane, in exhaled breath condensate 191
'isotime' measurements 73–74
ivacaftor 735

J

jackhammer oesophagus 703
Japanese summer-type hypersensitivity pneumonitis 557, 560
joints
    cystic fibrosis-related disease 737
    tuberculosis 436

K

Kaposi sarcoma 688
'keel chest' *see* pectus carinatum (PC)
ketoconazole 493
kidney cancer, endobronchial metastases 497
King's Sarcoidosis Questionnaire 564
Kinyoun stain 7, 8, 202
KIT amplification 450
Klebsiella (spp.), descending necrotising mediastinitis 672
Klebsiella pneumoniae, aspiration pneumonia 412
KRAS gene mutations, lung cancer 449, 450, 453

L

lactate dehydrogenase (LDH) 435, 663
lactate threshold 72
lactic acidosis 74
Lady Windemere syndrome 443
'lambda' sign 182
Lambert-Eaton syndrome 456

Langerhans cell(s) 14, 581
  giant cells 565
  immunohistochemistry 582
  in pulmonary LCH 582
Langerhans cell histiocytosis (LCH) 581
  adult pulmonary 581–584
    chest imaging 582, 583
    clinical features 582
    diagnosis 583
    differential diagnosis 582
    epidemiology 581
    evolution 583–584
    lung function tests 583
    management 584
    pathology 582
    pathophysiology 581–582
  BAL fluid markers 140, 583
laninamivir, influenza treatment 395
lanreotide 492–493
large B-cell lymphoma 16, 516
large cell carcinoma 15
laryngeal amyloidosis 593
laryngeal atresia 365–366
laryngeal cleft 367
laryngeal cyst 367
laryngeal web 366
laryngocele 367
laryngomalacia 366–367
laryngopharyngeal reflux 704
laryngotracheal tube 6
laryngo-tracheo-oesophageal cleft 367
larynx
  congenital anomalies 365–367
  infantile (laryngomalacia) 366–367
latent tuberculosis infection (LTBI) 418, 438–441
  controversies 440
  detection 421, 439, 688
    contact investigation 439, 440
    timing 439
  in HIV infection 687–688
  pathophysiology 418
  prophylaxis in HIV infection 687–688
  reactivation in immunocompromised patients 430–431, 440
  screening 431, 439–440
  TB prevention 439, 440
  TB risk 418, 438–439
  treatment 426, 431, 439, 440
lateral chest radiograph 155
lateral decubitus chest radiograph 155
left heart disease, pulmonary hypertension 629, 630, 633
left ventricular afterload, nasal CPAP reducing 526
left ventricular ejection fraction (LVEF), reduced
  pulmonary hypertension due to 629, 630
  sleep apnoea 530
left ventricular failure
  Cheyne–Stokes respiration 530
  transthoracic ultrasound 163
Legionella (spp.)
  community-acquired pneumonia 379
  diagnostic approach 195
  serological tests 198
  staining method 11
Legionella pneumophila serogroup 1, urinary antigen 197
Legionnaire's disease 197
LENT score 507, 664
leptin 537
letermovir 390
leukaemia
  acute, pulmonary infections in 707, 709
  acute myeloid 16
  acute promyelocytic 17, 710, 712
  chronic lymphocytic 707–708, 710
  chronic myeloid 712
leukocyte adhesion deficiency (LAD) 403
leukostasis 711
leukotriene(s), in exhaled breath condensate 191
leukotriene receptor antagonists *see* antileukotrienes
levofloxacin
  COPD exacerbations 335
  cystic fibrosis 731
  extrapulmonary tuberculosis 434
  pneumonia 381, 386
  pulmonary tuberculosis 422
Lhermitte's syndrome 488
light-emitting diode (LED) technology 202
Light's criteria 663
linear regression 769
line probe assay (LiPA) 205
linezolid therapy, pulmonary tuberculosis 423
lingula 3
lipid pneumonia 13
lipoid pneumonia, drug-induced 599, 611
liver disease
  α_1-antitrypsin deficiency 745
  cystic fibrosis 735, 736
  detection 705
  lung disease with 701–706
lobar bronchi 3
lobectomy
  angioplastic 477
  bronchoplastic 476, 477
  lung cancer 473, 475
  post-operative mortality 475
  pre-operative assessment 94
  pulmonary carcinoids 492
  sleeve, in lung cancer 476
Löfgren syndrome 563, 564
logistic regression model 769
long-acting antimuscarinics (LAMA) 346
  COPD 329, 346
    exacerbation prevention 337
  see also anticholinergic therapy
long-acting β_2-agonists (LABA) 345
  asthma management 317, 346
  COPD management 329, 345, 346
    exacerbation prevention 337
longitudinal study 757, 759

  - non-crossover 759
- long-term oxygen therapy (LTOT) 254–255
  - adult pulmonary Langerhans cell histiocytosis 584
  - assessment for 254
  - in bronchiectasis 270
  - COPD 254, 270, 329
  - criteria in steady-state patients 254, 255
  - indications 254
  - problems, in COPD 254
- long-term ventilation (LTV) 266–272
  - definition 266
  - discharge planning and follow-up 271
  - indications 266
  - pathophysiology 266
  - prevalence of use 266
  - in specific diseases
    - bronchiectasis 270
    - central hypoventilation syndromes 269–270
    - chest wall disorders 268
    - COPD 270
    - cystic fibrosis 270
    - interstitial lung disease 271
    - neuromuscular diseases 268–269
    - spinal cord injury 269
    - tracheostomy 267–268
  - types 267
  - ventilators 267
    - interfaces 267
- lordotic chest radiograph 157
- losartan 217
- lower respiratory tract infections (LRTIs)
  - diagnosis 196
  - environmental tobacco smoke exposure 776
  - viral 198
    - nucleic acid amplification tests 198
  - *see also* respiratory infections; specific infections
- LTBI *see* latent tuberculosis infection (LTBI)
- lumacaftor 735
- lung(s)
  - anatomy 1, 2–5
  - apex 2
  - barotrauma 783, 784
  - base 2
  - chest radiograph 156
  - collapse 666
  - consolidation *see* consolidation, lung
  - CT *see* computed tomography (CT)
  - cytology *see* cytology
  - deformability 51
  - elastance (EL) 51
  - expansion 666
  - functions 541
  - histology 301
  - left 2, 3
  - lobes 2, 3
  - pressure–volume curves 84
  - protection, ARDS management 302
  - resections *see* pulmonary resection
  - resistance, measurement 51
  - right 2, 3
  - segments 3
  - shadowing, in pneumonia 377, 378
  - topographic anomalies 370
  - transbronchial biopsy 128
  - trapped 513
  - ultrasound 166–167
  - volume *see* lung volume(s)
- lung abscess 278–281
  - bacteriology and culture 279–280
  - cause and risk factors 278
  - cavitating 279
  - clinical features 278–279
  - diagnosis 278–279
  - fungi causing 279
  - imaging 279
  - management 280
  - outcome 281
  - ultrasound 167
- lung adenocarcinoma *see* adenocarcinoma, lung
- ‘lung age,’ smoking cessation and 264
- lung biopsy 207–209
  - cryobiopsy 130, 208
  - cryo-bronchial 128, 130
  - HRCT to determine location 176, 178
  - in specific diseases
    - eosinophilic granulomatosis with polyangiitis 640
    - idiopathic interstitial pneumonias 572, 573
    - interstitial lung disease 724
    - Langerhans cell histiocytosis 583
    - lung cancer 456
    - lymphangioleiomyomatosis 587
    - peripheral lesions 208–209
    - pulmonary alveolar proteinosis 590
    - sarcoidosis 565
  - transbronchial *see* transbronchial lung biopsy
  - transthoracic, pulmonary nodules 503
- lung cancer 447–489
  - adenocarcinoma *see* adenocarcinoma
  - age at diagnosis 461
  - central tumours, SBRT toxicity 488
  - clinical manifestations 115, 456
  - diagnosis/investigations 456–457
    - endobronchial ultrasound 129–130, 456, 460
    - PET/CT 183–184
    - pulmonary function tests 460–461
    - transbronchial fine-needle aspiration 456
  - early-stage
    - defining 473
    - survival based on 482
  - epidemiology 453–454
    - smokers *vs* nonsmokers 453–454
  - follow-up after treatment 461
    - FDG-PET/CT 184, 185
  - functional assessment 460–461
  - in HIV infection 688
  - interventional pulmonology 132
  - locally advanced
    - radiotherapy 481
    - survival and treatment 482

  ‘local recurrence’ 476
  locoregional spread, staging 459
    guidelines 460
  lymph node involvement risk 459–460
    staging 460
  lymph node metastases
    after surgery 476
    mediastinal 5, 459, 460
  management *see* lung cancer treatment
  metastasis 495, 496
    in bone 499
    clinical features 456
    distant, FDG-PET/CT 184
    distant, sites 456, 495, 498, 499
    nodal *see above*
    osteolytic 498, 499
    staging 457
    treatment 463
  molecular genetic abnormalities 447–451, 453
    ALK 449–450, 467
    BRAF 449
    ‘driver’ mutations 447, 464
    EGFR 447, 448, 464–465
    EGFR (exons 19 and 21) 448, 465
    EGFR (T790M mutation) 448–449, 465, 466
    EMLA4 449, 467
    ErbB family 448
    FGFR1 451
    HER2 and *HER4* 449
    KIT amplification 450
    KRAS 449, 450, 453
    MET 450, 466
    nonsmokers 448
    percentages 448
    PIK3CA 450–451
    RET 450
    ROS1 450
    as treatment targets 464–467, 469, 470
  molecular testing 447–448, 456–457
    interpretation and consensus statements 447–448
  N1 disease 457, 458, 460
    surgery, survival rates 474
  N2 disease 457, 458, 460, 473, 476
    lymph node dissection 476
    minimal N2, definition 473
    surgery, survival rates 474
    surgery *vs* radiochemotherapy 472–473
    survival/prognosis 473
  in never-smokers 454
  in nonsmokers 447, 454
  NSCLC *see* non-small cell lung cancer (NSCLC)
  occupational 748, 752
  paraneoplastic effects 456
  pathogenesis, smokers 453–454
  pathology 456–457
  pericardial effusion 495–496
  predictive markers 448, 451
    PD-L1 expression 230
  prognosis 447
    by stage 459
  relapse, risk 461
  restaging after treatment, FDG-PET/CT 184
  risk factors
    air pollution 454, 774, 776
    asbestos 752
    environmental exposures 454, 776
    environmental tobacco smoke 776
    smoking 259, 453–454, 755
  SCLC *see* small cell lung cancer (SCLC)
  screening 454–455
    low-dose CT 170
  second primary, risk 461
  squamous cell carcinoma *see* squamous cell carcinoma
  stage I disease
    lymph node dissection 476
    surgery, survival rates 473
  stage II disease, surgery, survival rates 474
  stage IIIA disease, surgery, survival rates 474
  stage IV disease, systemic treatment 463
  staging 457–460
    FDG-PET/CT 184
    IASLC grouping algorithm 457, 458
    mediastinal, ESMO 5, 459, 460
    outcome by stage 459
    TNM classification 457, 458
  survival (5-year)
    after bronchoplastic lobectomy 477
    after lymph node dissection 476, 477
    after surgical treatment 473–474, 477
  symptoms and signs 115, 456
lung cancer treatment 463–471
  chemotherapy 463, 464
  chemotherapy drugs, considerations 466
  immune checkpoint inhibitors 227–231, 451, 464, 467–468, 469
    anti-PD-1 and PD-L1 inhibitors 227, 228, 229, 467, 469
    CTLA4 blockade 227–228, 229, 467–468
  molecular biological 464
  NSCLC *see under* non-small cell lung cancer (NSCLC)
  optimal (surgical) 473
  palliative 463, 470
  performance status scales 464, 466
  radiotherapy *see* radiotherapy
  SCLC *see* small cell lung cancer (SCLC)
  surgical 472–480
    alternatives to 472
    complete anatomic resection 475
    complete homolateral lymph node dissection 475–476
    en bloc R-0 resection 475
    follow-up after 461
    hospital volume impact 474, 475
    lobectomy 475
    minimally invasive surgery 477–478
    pneumonectomy 475
    pneumonectomy alternatives 476–477

    - post-operative complications 476, 477
    - post-operative mortality 474, 475
    - pre-operative assessment 95
    - principles 475–476
    - quality requirements 474–475
    - radiochemotherapy *vs* 472–473
    - survival (5-year) 473–474, 477
    - work-up 473
  - targeted 464–467
- lung compliance (*C*L) 30, 31, 32, 38, 51
  - measurement 51–52
- lung congestion, chronic, spirometry in 695–696
- lung cysts
  - lymphangioleiomyomatosis 585, 586, 587
  - ultrasound 167
- lung disease
  - diagnosis in cardiac disease 696–698
    - COPD underdiagnosis, reasons 694–696
    - flowchart 697
  - at high altitude 782
  - measuring occurrence and causation 753–770
    - *see also* epidemiological studies
  - occupational *see* occupational diseases
  - *see also* specific diseases
- lung function testing *see* pulmonary function tests
- lung hyperinflation *see* hyperinflation (lung)
- lung injury
  - acute *see* acute lung injury (ALI)
  - arterial blood gas analysis 62
  - secondary 300
- lung recoil 30, 32, 33, 48
  - decrease in disease 84
  - lung volumes and 48, 84, 85, 86
  - recoil pressure (PREC) 32, 33, 48
- LUNG-SAFE study 302
- lung scintigraphy *see* scintigraphy
- 'lung sliding' sign 162, 166
- lung transplantation 288–292
  - age limitation 289
  - aims 288
  - bilateral *vs* single lung, idiopathic interstitial pneumonias 579
  - complications/post-operative problems 290–291
    - bronchial anastomotic problems 133, 291
    - bronchial stenosis 133
    - chronic lung allograft dysfunction 290, 291
    - obliterative bronchiolitis 413
    - opportunistic infections 406, 407
    - primary graft dysfunction 290–291
    - rejection 291
    - respiratory virus infections 199, 407
  - contraindications 288, 289, 738
  - donor organs 290
  - history 288
  - immunosuppressive drugs 291
  - indications 288–289
  - patient selection 288–289, 738
  - sequential single (SSLTx) 290
  - in specific conditions 288–289
    - adult pulmonary Langerhans cell histiocytosis 584
    - α_1-antitrypsin deficiency 746
    - COPD 329
    - cystic fibrosis 288, 290, 738
    - idiopathic interstitial pneumonias 578–579
    - lymphangioleiomyomatosis 588
  - surgical procedure 290
  - timing, idiopathic interstitial pneumonias 578
- lung tumours
  - carcinoid *see* pulmonary carcinoids
  - chest wall invasion 120
  - cytology 14–16
  - lymphoid 16
  - metastatic 496–498
  - pneumocytomas 493–494
  - pulmonary hamartomas 493
  - ultrasound 166–167
  - *see also* lung cancer
- lung volume(s) 83–89
  - in asthma 312
  - in COPD 718
  - determinants 83–87
  - dynamic 83, 88
  - elastic recoil and 48, 84, 85, 86
  - measurement 87–88
  - normal values 88
  - obesity effect 717, 718
  - obesity hypoventilation syndrome 537
  - reduction
    - by diving 784
    - drug-induced respiratory disease 602
  - static 83, 88
- lung volume reduction coils (LVRCs) 283, 284–285
- lung volume reduction surgery (LVRS) 251, 282
  - assessment for 326
  - COPD 329
  - definition 282
  - emphysema 95, 326
- lupus, drug-induced 603, 604, 609
- Lutetium-177 492
- lymphadenitis, tuberculous 434
- lymphadenopathic Kaposi sarcoma 688
- lymphadenopathy
  - amyloid 594
  - drug-induced, hilar lymph nodes 603
  - mediastinal *see* mediastinal lymphadenopathy
- lymphangiitic carcinomatosis of lung 497–498
- lymphangioleiomyomatosis (LAM) 585–588
  - clinical features 586
  - diagnosis 586–587
  - differential diagnosis 586
  - epidemiology 585
  - evolution and prognosis 587
  - genetics 585
  - imaging 586
  - lung function tests 586
  - pathology (lung) 585–586
  - treatment 587–588
    - non-pharmacological 588
    - pharmacological 587–588

- lymphangioleiomyomatosis (LAM) cells 585, 586
- lymphatic drainage
  - lungs 4–5
  - mediastinum 5
  - pleura 1
- lymph node(s)
  - benign *vs* malignant, transthoracic ultrasound 164
  - hilar *see* hilar lymph nodes
  - intrapulmonary 502
  - mediastinal *see* mediastinal lymph nodes
  - tuberculosis 434
- lymph node dissection
  - lung cancer 475–476
  - pulmonary carcinoids 492
- lymphocytes
  - airway inflammation 20–21
  - in BAL fluid 140, 142
  - hypersensitivity pneumonitis 557
  - *see also* B-cell(s) (B-lymphocytes); T-cell(s) (T-lymphocytes)
- lymphocytic interstitial pneumonitis, in HIV infection 689
- lymphocytosis 13
- lymphoepithelial complexes 17
- lymphoid follicles, in airways, in COPD 21, 22
- lymphoid interstitial pneumonia (LIP)
  - in HIV infection 689
  - in primary antibody deficiency (PAD) 677
  - *see also* idiopathic interstitial pneumonias (IIPs)
- lymphoid tumours, primary, of lung 16
- lymphoma
  - affecting lung 16
  - B-cell 16, 688
    - in HIV infection 688
  - bronchial-associated lymphoid tissue 678, 724
  - chest wall involvement 507
  - in HIV infection 688
  - large cell non-Hodgkin 16, 516
  - lymphoblastic non-Hodgkin 516
  - mediastinum involvement 515, 516
    - histological diagnosis 518, 519
  - natural killer T-cell 16
  - pleural metastases 495
  - in primary immunodeficiency 677
  - pulmonary, in primary immunodeficiency 677
  - sarcoidosis *vs* 182
- lymphoproliferative disorders
  - cytology 16–17
  - pulmonary infections 709

M

- M2 ion channel inhibitors, influenza treatment 395
- macitentan 577
  - pulmonary arterial hypertension 634
- macrolide antibiotics
  - bronchiectasis exacerbation reduction 356
  - COPD exacerbation prevention 329, 337, 351
  - side-effects 351, 356
- macrophage(s) 9
  - airway inflammation 20–21, 24
  - alveolar *see* alveolar macrophages
  - ARDS pathophysiology 301
  - in COPD 24
  - empty vacuoles 13
  - foamy 13, 606
  - IL-17A expression 21
  - iron-laden 12
  - *M. tuberculosis* infection 417, 418
  - normal sputum 188, 189
  - phagocytosis by 24
  - phenotypes, in COPD 24
  - smokers' 13
- macrophage inflammatory protein-1α 25
- magnetic resonance imaging (MRI) 171–173
  - chest 169
  - chest CT *vs* 169, 171
  - diffusion-weighted 173
  - indications 172
    - chest pain investigation 109
    - malignant pleural effusions 510
    - mediastinal tumours 516–517
    - pleural effusion 510, 661
    - pulmonary arteriovenous malformations 648
    - pulmonary embolism 172–173
    - tuberculous meningitis 435
  - principle 171–172
  - pulmonary ventilation imaging 173
- malakoplakia 11
- male reproductive tract, cystic fibrosis-related disease 730, 737
- malignant pleural effusion (MPE) 495, 507, 660–661
  - cancers associated 507
  - clinical signs 508–509
  - diagnosis 508–511
    - biopsies 510–511
    - cytology 510
    - imaging 510
    - medical thoracoscopy/pleuroscopy 148, 149
    - thoracocentesis 510
    - transthoracic ultrasound 165, 166
  - epidemiology 660, 661
  - incidence 507
  - management 507–508, 509, 512–513, 664
    - indwelling pleural catheters 513
    - talc pleurodesis 512, 513
  - pleural metastases and 495, 507, 510
  - prognostic factors 507
  - symptoms 506
- malignant pleural mesothelioma (MPM) 506–507
  - cytology 18
  - diagnosis 511
  - endoscopy 146
  - epidemiology and pathogenesis 506
  - pre-therapeutic assessment 511
  - staging 511
  - transthoracic ultrasound 164–165
  - treatment 470, 511–512
    - chemotherapy 470, 512
- malondialdehyde, in exhaled breath condensate 191

malt worker's lung 560
mammalian target of rapamycin (mTOR) inhibitors 492
  adverse effects 586, 598
  lymphangioleiomyomatosis 588
mandibular advancement devices (MADs) 527
mannitol challenge test 81
Mantoux test 421
manual aspiration of air, spontaneous pneumothorax 668–669
MAPK (mitogen-activated protein kinase) 448, 450, 582
maple bark stripper's lung 560
masks, noninvasive ventilation 267
Masson bodies 13
mast cell(s) 615
  in allergic response 223
  mediators, β_2-agonists inhibiting release 345
maxillomandibular advancement osteotomy 527
maximal achievable ventilation (MVV) 73
maximal incremental exercise testing 70–71
maximal insufflation capacity (MIC) enhancement 237
maximal oxygen uptake (peak $V'O_2$) 71–72, 75
  lung cancer 461
maximal voluntary ventilation (MVV) 83
May–Grünwald–Giemsa (MGG) stain 7, 8, 140
measles pneumonia, cytology 12
mechanical insufflation–exsufflation 237
mechanical ventilation
  acute-on-chronic respiratory failure 544
  in ARDS 302
  hospital-acquired pneumonia risk factor 384
  long-term *see* long term ventilation (LTV)
  noninvasive *see* noninvasive ventilation (NIV)
  respiratory mechanics measurement 52
  thoracentesis relative contraindication 153
mediastinal adenopathy 617
mediastinal amyloid lymphadenopathy 594
mediastinal cysts 515
  management 518–519
mediastinal drainage 673
mediastinal fibrosis 673–674
mediastinal infections 671
mediastinal lymphadenopathy 515
  amyloid 594
  chest pain 109
  drug-induced reaction 603
mediastinal lymph nodes 5
  classification 5
  lung cancer staging 459, 460
  metastatic tumours 498
  sarcoidosis diagnosis 565
mediastinal pleura 1
mediastinal space 1
mediastinal tumours 514–521
  benign 515
  diagnostic methods 516–518
  germ cell 17
  histological diagnosis 518
  histological types 514, 515
  malignant 515
  metastatic 514
  paraneoplastic syndromes 515
  surgery 518–519
  symptoms 515–516
  therapeutic strategies 518–520
  tumour markers 517–518
mediastinitis 671–674
  acute 671
  descending necrotising *see* descending necrotising mediastinitis (DNM)
  fibrosing 673–674
mediastinoscopy, lung cancer 460
mediastinum
  anatomy 5, 514
  chest radiograph 156
  intraoperative exploration in lung cancer 476
  paravertebral (posterior) 514
  prevascular (anterior) 514
  visceral (middle) 514
medical history 117, 118
Medical Research Council (MRC) dyspnoea scale 99
medical thoracoscopy/pleuroscopy (MT/P) 135, 145–150
  advantages 149
  chest ultrasonography before 146–147
  complications 149–150
  contraindications 149
  definition 145
  indications 145, 146, 149
    malignant pleural effusions 511
    malignant pleural mesothelioma 511
    pleural cancers 146
  instruments 148
  safety profile 149–150
  techniques 146–149
megakaryocytes 10
melanoma
  CTLA-4 antibodies 467, 468
  endobronchial metastases 497
  metastatic nodules on parietal pleura 146
membranous subglottic stenosis 366
Mendelson's syndrome 411
meningitis, tuberculous 434, 435
mepolizumab 350, 618
  pulmonary vasculitis 644
mercury embolism 603
MERIT-1 study 636
mesenchymal cells, idiopathic interstitial pneumonias 569
mesenchymal tumours, cytology 18
mesothelial cells 10
mesothelioma *see* malignant pleural mesothelioma (MPM)
mesothelium 10
metabolic acidosis 63, 64, 66
  causes 65, 68
metabolic alkalosis 63, 64, 66
  causes 65, 67

  kidney response 67
  renal ammoniagenesis role 66, 67
metabolic rate, ventilatory response during exercise 74
metabolic syndrome 525, 527
metal grinding, hypersensitivity pneumonitis 560
metastatic tumours 495–500
  in bone 498–499
  chest wall 489–499, 507
  hilar and mediastinal lymph nodes 498
  pericardial effusions 495–496
  pericarditis 495–496
  pleural *see* pleural metastases
  pulmonary 496–498
  see also specific tumour types and sites
metformin 220
MET gene amplification, lung cancer 450, 466
methacholine provocation test 77, 78, 79
  in asthma 104
methaemoglobin 610
methaemoglobinaemia 610
methicillin-resistant *Staphylococcus aureus*
  hospital-acquired pneumonia 384
  lung abscess 280
methotrexate
  asthma 351
  pneumonitis 606
  pulmonary vasculitis 643
methylprednisolone
  asthma exacerbation treatment 348
  COPD exacerbation treatment 336
MET inhibitors 450
c-MET pathway 450
mevalonate pathway 217, 218
Michaelis-Gutmann bodies 11
microaspiration, of gastric acid 411, 578
microbiological testing 194–200
  culture techniques *see* culture techniques
  Gram stain 7, 8, 196
  lower respiratory tract infections 194, 195
  NAATs *see* nucleic acid amplification tests (NAATs)
  primary care setting 194
  pulmonary tuberculosis 419–420
  rapid antigen tests *see* rapid antigen tests
  serology 197–198
  sputum *see* sputum
microscopic polyangiitis (MPA) 637
  epidemiology 637
  haemoptysis 115
  investigations 641–642
  pathology 641–642
  treatment 642–644
microscopy, TB diagnosis 202
midazolam 126
Middle East respiratory syndrome 397–399
  clinical features and diagnosis 398, 399
  epidemiology 397
  management 398–399
  transmission and virology 397–398
Middle East respiratory syndrome coronavirus (MERS-CoV) 397, 398
miliary patterns
  drug-induced respiratory disease 602
  tuberculosis 435
minimally invasive surgery, lung cancer 477–478
minute ventilation (V'_{E}) *see* V'_{E} (minute ventilation)
mitogen-activated protein kinase (MAPK) 448, 450, 582
mitomycin, metabolism in lung cells 598
mixed connective tissue disease (MCTD)
  clinical features 723, 725
  epidemiology 722
molecular biology
  lung cancer therapy 464
  pulmonary tuberculosis diagnosis 420
mollusc-shell hypersensitivity 560
monoclonal antibodies 408
  to interleukins 307, 350
  see also specific monoclonal antibodies
montelukast 349
Moraxella catarrhalis
  primary ciliary dyskinesia 743
  in primary immunodeficiency 675, 676
mortality *see* specific diseases
motility agents, chronic cough management 112
motivational interviewing, smoking cessation 263
motor cortex, dyspnoea 98, 100
motor neurone disease (MND)
  long-term ventilation 268, 269
  respiratory muscle weakness 653–654
  sleep-related hypoventilation syndromes 538
mould exposure 776
Mounier-Kuhn syndrome 361
moxifloxacin therapy
  COPD exacerbations 335
  nontuberculous mycobacterial infections 445
  pulmonary tuberculosis 422
mTOR inhibitors *see* mammalian target of rapamycin (mTOR) inhibitors
MT/P *see* medical thoracoscopy/pleuroscopy (MT/P)
MUC5B gene 554
MUCB gene 569
mucociliary clearance
  failure, primary ciliary dyskinesia 740
  impaired 355
  mechanism 741
mucoepidermoid carcinoma 16
mucolytics
  antioxidant 114
  chronic bronchitis 321
  COPD 329
    exacerbation prevention 337
mucorales, pneumonia due to 391
mucosa-associated lymphoid tissue (MALT) lymphomas 16
mucus 10
  hypersecretion 114–115
    chronic bronchitis 321
  impaction, therapeutic bronchoscopy 131

  - inspissated 10
  - plugging, bronchiectasis 354
- mucus clearance physiotherapy 234, 235
- multidrug-resistant (MDR) pathogens 383
  - hospital-acquired pneumonia 383, 385
    - treatment recommendations 386–387
  - new drug treatment 387
  - ventilator-associated pneumonia 385
- multidrug-resistant tuberculosis (MDR-TB) 201, 205, 416
  - countries with high burden 425
  - epidemiology 418–419
  - treatment recommendations 421, 424, 425
- multiple endocrine neoplasia type 1 (MEN-1) 490
- mupirocin ointment 307
- muscle disorders, hypercapnic respiratory failure due to 543
- muscle fatigue 243
- mushroom worker's lung 560
- myasthenia gravis (MG) 515, 518, 520
  - detection 656
- mycobacteria 203
  - antigens, detection 421
  - characteristics 417
  - culture techniques 420
  - detection methods 420, 421
  - genes 417
  - immune response to 438, 439
  - nontuberculous *see* nontuberculous mycobacteria (NTM)
  - species 416–417
  - staining method 11
  - structure 417
  - tuberculous 203
    - *see also Mycobacterium tuberculosis*
- Mycobacteriaceae 416–417
- mycobacterial infections
  - immunocompromised hosts 389
    - primary immunodeficiency 676
  - laboratory diagnosis 201–205
    - culture 203, 420
    - 'decontamination' 202
    - drug susceptibility testing 204–205, 390, 419, 420, 421
    - identification of species 203–204
    - laboratory service organisation 206
    - microscopy 202
    - molecular detection 202–203
    - molecular detection of resistance 205–206
    - specimen procurement, transport, processing 202
    - turnaround times for identification 204
  - TB *see* tuberculosis (TB)
- *Mycobacterium* (genus) 203
- *Mycobacterium abscessus* 442, 444, 738
  - treatment 445
- *Mycobacterium avium* complex (MAC) 444
  - hypersensitivity pneumonitis 443–444
  - treatment 445
- *Mycobacterium bovis* 417, 427
- *Mycobacterium kansasii* 443, 444
  - treatment 445
- *Mycobacterium leprae* 442
- *Mycobacterium malmoense*, treatment 445
- *Mycobacterium simiae*, treatment 445
- *Mycobacterium szulgai*, treatment 445
- *Mycobacterium tuberculosis* 416
  - contacts, risk of TB 438, 439
  - detection 439
  - drug susceptibility testing 204–205, 390, 419, 420, 421
  - immune response to 417–418, 429
  - infection *see* tuberculosis (TB)
  - infection route 417
  - MDR-TB *see* multidrug-resistant tuberculosis (MDR-TB)
  - multiplication 418
  - spread 436
  - structure 417
  - transmission 417, 421, 438
  - XDR *see* extensively drug-resistant TB (XDR-TB)
- *Mycobacterium tuberculosis* complex (MTC) 201, 203, 416–417, 442
  - drug-resistance detection 204–205
    - molecular detection 205–206
  - molecular detection 202–203
  - species included 203
  - turnaround times for identification 204
  - *see also* mycobacterial infections; tuberculosis (TB)
- *Mycobacterium xenopi* 444
  - treatment 445
- mycolic acid 417
- *Mycoplasma*, community-acquired pneumonia 379
- *Mycoplasma pneumoniae* infection
  - community-acquired pneumonia 379
  - diagnostic approach 195
  - serological tests 197–198
- myeloid disorders, cytology 16–17
- myeloma 708, 710
- myeloperoxidase (MPO) 637
- myocardial infarction, COPD with 692

N

- NALP7 21
- nanoparticles, air pollutants 777
- 'napkin ring cartilages' 369
- nasal continuous positive airway pressure (nCPAP)
  - control of breathing and 526
  - heart and 526
  - metabolic/systemic effects 527
  - obstructive sleep apnoea 525–527
  - upper airway and 526
- nasal decongestants 375
- nasal polyps 306
  - asthma association 315
  - chronic rhinosinusitis with 305–306, 307
  - in cystic fibrosis 730
  - in eosinophilic granulomatosis with polyangiitis 638

    surgical management 307
nasopharyngeal airway, congenital malformations 364–365
natural killer (NK) cells 23
    toxicity, in COPD 23
natural killer T-cell lymphoma 16
nausea and vomiting, chemotherapy-induced 465
nebulisers 212, 214
    direct bronchial provocation testing 78, 79
necroptosis 26
necrosome 26
negative predictive value (NPV) 767, 768
nerve supply, airways 3–4
net acid excretion (NAE) 67
netarsudil 222
neuralgic amyotrophy 653, 658
neuralgic pain, chest 109
neuraminidase (N) 393
neuraminidase inhibitors
    influenza treatment 395
    resistance 396
neuroendocrine tumours 490, 491
'neurogenic inflammation' 216
neuromechanics, increase in ventilation 98, 100
neuromuscular blockers, in ARDS 302
neuromuscular diseases (NMD) 653–659
    acute respiratory failure 294, 296, 298, 653
    causes 653–654
    central sleep apnoea 533
    diaphragm weakness *see* diaphragm, weakness
    dyspnoea 101–102, 653
    hypercapnic respiratory failure due to 543
    long-term ventilation 268–269
    noninvasive ventilation in 548, 549
    respiratory muscle weakness 653–654
    respiratory physiotherapy 236–237, 658
    sleep-related hypoventilation syndromes 538, 539, 657
neuropathy, chemotherapy-induced 465
neurophysiology
    chest pain 108
    dyspnoea 97, 98
neuroventilatory dissociation (NVD) 97, 101, 102
neutropenia
    chemotherapy-induced 465
    pulmonary infections in 388, 389, 391, 405, 707, 708
        Aspergillus pneumonia 391
        diagnosis 405
        severity and duration, risks 707, 708
neutrophil(s)
    airway/lung inflammation 20–21, 25
        asthma 322
        COPD 25, 188, 189, 325
    ARDS pathophysiology 301
    in BAL fluid 142
    IL-17A expression 21
    serine proteinase inhibitors 744
    in sputum, in COPD 188
neutrophil activating protein-2 25
neutrophil extracellular traps (NETs) 25
neutrophilia
    in COPD 23, 25
    sputum 188, 189
neutrophilic microabscess 641
next-generation sequencing (NGS), lung cancer 447
    resistance to EGFR TKIs 448
NICE guidelines
    endoscopic treatment of emphysema 135
    interventional endobronchial treatments 133
nicotine 258, 259, 261
    addiction, carcinogens, lung cancer link 453, 454
nicotine replacement therapy (NRT) 263–264
nintedanib 182, 467, 470, 556
    idiopathic interstitial pneumonias 577
    idiopathic pulmonary fibrosis 555, 577
nitinol coils 283, 284–285
nitrates, in exhaled breath condensate 191
nitric oxide
    alveolar uptake rate (*K*NO) 57–58
    exhaled fraction *see* *F*ENO (exhaled nitric oxide fraction)
    inhaled
        in ARDS 302
        pulmonary arterial hypertension diagnosis 634
    nasal, primary ciliary dyskinesia 355, 741
    oxidative stress and 777
    production, hepatopulmonary syndrome 704
nitrites, in exhaled breath condensate 191
nitrofurantoin
    lung toxicity 599
    metabolism in lung cells 598
nitrogen, diving and 784
nitrogen dioxide, air pollution 772, 773
nitrogen washout method 88
nitrosothiol, in exhaled breath condensate 191
nitrotyrosine, in exhaled breath condensate 191
NIV *see* noninvasive ventilation (NIV)
nivolumab 227, 228, 467
    NSCLC 467, 468
NLRP3 26
Nocardia, staining method 11
nocturnal desaturation 254
nocturnal hypoventilation 266, 269, 270, 535–536
nodular bronchiectasis 443
nodules, pulmonary *see* pulmonary nodules
nominal scale 753, 754
noninvasive ventilation (NIV) 266, 267
    acute service provision 551
    contraindications 547, 548
    failure, primary/secondary 550–551
    failure rates 550–551
    guidelines on use 546
        implementation 551
    high-flow nasal cannula (HVNC) therapy *vs* 256, 551
    indications 546, 547, 548, 549
    initiation criteria 549
        in acute COPD 547
    levels of evidence for use, in ARF 546, 547

  monitoring 548
  nocturnal 550
    obesity hypoventilation syndrome 538
  oxygen therapy and 254, 255
  practicalities of ventilator settings 547, 548, 549
  simulator 551
  in specific conditions 546, 547, 548, 549
    acute cardiogenic pulmonary oedema 546, 550
    acute exacerbations of COPD 544, 546, 547, 549, 550
    acute hypercapnic respiratory failure 546–549, 550
    acute hypoxaemic respiratory failure 549–550
    acute pulmonary oedema 549
    acute respiratory failure 546–552
    ARDS 302
    bronchiectasis exacerbation 549
    COPD 270, 544, 546, 547, 548
    cystic fibrosis 549
    hypercapnic respiratory failure 546–549, 550
    hypoventilation syndromes 539
    hypoxaemic respiratory failure 549–550
    neuromuscular disease 268–269, 539, 549, 658
    obesity hypoventilation syndrome 269–270, 538, 549
    pneumonia 380, 549–550
  stopping 550–551
  withdrawal 550
non-small cell lung cancer (NSCLC)
  early stage 459
    nivolumab neoadjuvant therapy 230
  histology, response to chemotherapy and 469
  locally advanced 459
    checkpoint inhibitor therapy 228
  metastatic
    checkpoint inhibitor therapy 228
    chemotherapy 469
    treatment advances 456
  molecular genetic abnormalities 449–450, 467, 469
    treatment selection 469, 470
  nonmetastatic, checkpoint inhibitor therapy 230
  nonsquamous, immunotherapy *vs* chemotherapy 229
  recurrent, immune checkpoint inhibitors 464
  squamous, immunotherapy vs chemotherapy 229
  stage I, treatment, stereotactic body radiation therapy 485
  stage II, treatment 469
    stereotactic ablative radiotherapy 484–485
    stereotactic body radiation therapy 484–485
  stage III, treatment 469
    chemoradiotherapy 483
    proton therapy 484
    radiotherapy 483–484
  stage IV, treatment 469
    elderly 460
    stereotactic body radiation therapy 486
    untreated, checkpoint inhibitors 228–229
  staging 457
    FDG-PET/CT 184, 185
    mediastinal, ESMO guidelines 459, 460
  surgical treatment 472
    alternatives to 472
    follow-up after 461
  survival, based on stage and treatment 482
  treatment 469–470
    anti-angiogenesis 467
    checkpoint inhibitors 227–229, 464, 467–468, 469
    checkpoint inhibitors *vs* docetaxel 228
    chemoradiotherapy 469, 483
    chemotherapy 464, 469, 470
    CTLA4 blockade 227–228, 467
    cytotoxic drugs and immunotherapy 228–229
    first-line 469
    nivolumab and pembrolizumab 227, 228, 467, 468
    PD-1 and PD-L1 inhibitors 227, 228, 467
    radiotherapy 482, 483–484
    second-/third-line 469–470
    by stage *see* stages above
    targeted therapy 464–467, 469, 470
    tyrosine kinase inhibitors 448, 466
  see also lung cancer
nonsmokers
  environmental tobacco smoke exposure 765, 766
  lung cancer risk 447, 453–454
  molecular genetics in lung cancer 448
nonspecific interstitial pneumonia (NSIP)
  in connective tissue diseases 723, 724
  diagnosis 572
  in HIV infection 689
  in primary antibody deficiency 677, 678
  in systemic sclerosis 723, 724
  see also idiopathic interstitial pneumonias (IIPs)
non-steroidal anti-inflammatory drugs (NSAIDs)
  adverse effects 597, 598
  upper respiratory tract infections 375
nontuberculous mycobacteria (NTM) 201, 442–446
  culture 444
  distinguishing features 442
  distribution 442
  in HIV infection 686
nontuberculous mycobacterial (NTM) infections 442–446
  chest radiography 445
  in cystic fibrosis 730, 733
    management 733
  epidemiology 442
  in HIV infection 443
  in immunodeficiency conditions 404, 443
  impaired immunity and 443
  laboratory diagnosis 444
  pathogenesis 442–443
  pulmonary disease 443–444
    diagnostic criteria 444
  testing, in bronchiectasis 355

  treatment 444–445
  tuberculin skin test 421
normochloraemic acidosis 65
nortriptyline 263
nosocomial infections
  in haematological diseases 708
  Middle East respiratory syndrome (MERS) 398
  pneumonia *see* hospital-acquired pneumonia (HAP)
  severe acute respiratory syndrome (SARS) 398
nosocomial pneumonia *see* hospital acquired pneumonia (HAP)
NTM *see* nontuberculous mycobacteria (NTM)
nuclear factor-κB 21, 220, 348, 404
nuclear medicine 181–186
  inflammatory disease diagnosis 182–183
  lung cancer diagnosis 183–185
  perfusion scanning *see* perfusion (Q') lung scintigraphy (PLS)
  pulmonary embolism diagnosis 181–182, 624, 625, 626
  ventilation (V') scanning 182, 624
  see also positron emission tomography (PET); scintigraphy
nucleic acid amplification tests (NAATs) 198–199
  extrapulmonary tuberculosis 434
  mycobacterial infection detection 203, 430
    drug resistance detection 205
  pulmonary tuberculosis diagnosis 420
  single-target or multiplex 198–199
  tuberculosis in HIV infection 686
null hypothesis 763
Nuss procedure 650, 651
nutrition supplements, palliative care 250–251

O

obesity 522, 716–721
  asthma 717–718
    management 721
  cardiomyopathy 720
  COPD and 245, 718–719
  definition (WHO) 716
  dyspnoea 103–104
  epidemiology 716
  ‘hyperinflators’ and ‘deflators’ (lungs) 103
  hypoventilation syndromes 535–536, 537–538
  lung function, effects on 717
  management 720–721
  pulmonary hypertension 720
  respiratory infections 719
  sleep-related breathing disorders 719
  thromboembolic disease 720
obesity hypoventilation syndrome (OHS) 269–270, 537–538, 719
  management 538
    noninvasive ventilation 269–270, 538, 549
oblique chest radiograph 157
oblique fissure 2
obliterative bronchiolitis
  clinical features and diagnosis 714
  drug-induced 609
  haematological disease association 714
  occupational aetiology 752
  post-transplant 413
observational studies 757, 758–759
obstructive apnoea
  diaphragm EMG 656, 657
  sleep-related *see* obstructive sleep apnoea (OSA)
obstructive lung disease
  functional residual capacity 86
  increased residual volume 85
  in primary immunodeficiency 676
  sleep-related hypoventilation syndromes 536, 539
  vital capacity, in diagnosis 86
  see also specific diseases
obstructive sleep apnoea (OSA) 719
  with Cheyne–Stokes respiration/central sleep apnoea 530
  COPD with (overlap syndrome) 254
  Duchenne muscular dystrophy 539
  epidemiology 719
  high altitude effect 782
  obesity 719, 720
    management 721
  obesity hypoventilation syndrome 537
  pulmonary hypertension and 720
  STOP-BANG screening tool 92
obstructive sleep apnoea–hypopnoea syndrome (OSAHS) 522–528
  assessment 523
  consequences 524–525
    cardiovascular 524–525
    metabolic 525
  definition 522–523
  diagnostic criteria 522
  pathogenic mechanisms 523
  pathophysiology 523–524
  prevalence 523
  treatment 525–527
    CPAP 525–527
    mandibular advancement devices 527
    non-CPAP treatment 527
    surgical 527
occupational asthma 749–750
  clinical features 750
  common causes 749
  definition 748
  diagnosis 750
  irritant-induced 748, 750
  management 750
  see also work-related asthma (WRA)
occupational diseases 748–752
  airway diseases 752
  asbestos-related pleural diseases 752
  asthma *see* occupational asthma
  compensation for 752
  epidemiology 748
  hypersensitivity pneumonitis *see* hypersensitivity

  - pneumonitis (HP)
  - lung cancer 752
  - pneumoconiosis 750–751
- occurrence, measurement *see* epidemiological studies
- octreotide, in pulmonary carcinoids 492–493
- octreotide scanning, pulmonary carcinoids 491
- ocular tuberculosis 437
- odds ratio (OR) 762–763, 768–769
  - relative risk relationship 763
- oesophageal atresia 368
- oesophageal disease
  - in cystic fibrosis 736
  - motility disorders 701, 702
- oesophageal peristalsis
  - absent 703–704
  - minor disorders 704
- oesophageal pH monitoring 412
- oesophageal pressure (P_{oes}), tidal 100, 102
- oesophageal spasm, distal 702
- oesophagitis, radiation-induced 488
- oesophagogastric junction outflow obstruction 702
- oesophagus
  - absent contractility 703–704
  - jackhammer 703
  - radiation toxicity 488
- oestrogens 587
- olodaterol 345
- omalizumab 350
- ‘one airway’ concept 315
- opiates/opioids
  - dyspnoea intervention 106
  - palliative care 250
- opportunistic infections 388, 400–410
  - *see also under* immunocompromised hosts
- ordinal scale 753, 754
- organic dust toxic syndrome (ODTS) 561
- organising pneumonia 13, 14
  - drug-induced 599, 607–608
  - *see also* cryptogenic organising pneumonia (COP)
- oropharyngeal infection 671
- orphan lung disease 585
- orthodeoxia 647, 705
- oseltamivir
  - influenza prophylaxis 395
  - influenza treatment 395
- osimertinib 448, 465, 467
- osteolytic metastases 498, 499
- otitis media 741
- outdoor pollution *see* air pollution
- overweight, epidemiology 716
- overwhelming post-splenectomy infection (OPSI) 409
- OX40 230
- oxidant–antioxidant balance, air pollution and 777
- oxidative stress
  - air pollutants inducing 777
  - in COPD 22, 23
  - genetic susceptibility 777
  - pollutant types causing 777
  - renin-angiotensin system generating 216
- oxitropium bromide 346
- oxygen
  - alveolar–arterial gradient ($P_{\text{A–aO}_2}$) 61–62
    - exercise testing and 75
    - hypoxaemia with hypoventilation 542
    - respiratory failure 542
  - alveolar tension (P_{AO_2}) 28, 29, 34, 36, 37
    - V'_{A}/Q' mismatch 38–39, 62
  - arterial desaturation 73, 75
    - obstructive sleep apnoea–hypopnoea syndrome 522
  - arterial saturation (S_{aO_2}) 253
    - oxygen therapy indication 253
    - *Pneumocystis jirovecii* pneumonia 684
    - pneumonia management 380
  - arterial tension (P_{aO_2}) 60, 61
    - acute respiratory failure (type 1) 293
    - ARDS criteria 299
    - blood gas analysis 60, 61
    - hepatopulmonary syndrome 705
    - hypoxaemic respiratory failure 62
    - normal 61
    - obesity hypoventilation syndrome 537
    - *Pneumocystis jirovecii* pneumonia 684
    - reference interval 61
    - respiratory failure 541
  - diffusion coefficient 35
  - diffusion limitation, hypoxaemia due to 61, 62
  - inspiratory fraction (F_{IO_2})
      - ARDS criteria 299
      - hypoxaemic respiratory failure 542
  - peak uptake (peak $V'_{\text{O}_2\text{peak}}$) 71–72, 75
    - lung cancer 461
  - transport 35
  - triggered acute ‘recall’ toxicity to drugs 598
  - uptake (V'_{O_2}) 28, 29
    - high altitude 780
- oxygen dissociation curve 29, 37, 38, 39, 61
- oxygen pulse 72
- oxygen therapy 253–256
  - acute 253
  - ambulatory 254
  - COPD exacerbation treatment 336, 547
  - decompression sickness 785
  - delivery systems 255
  - entrainment into NIV/CPAP circuits 255–256
    - acute hypercapnic respiratory failure 547
    - acute hypoxaemic respiratory failure 550
    - COPD exacerbations 547
  - high-concentration 253
  - high-flow nasal cannula 255–256
    - noninvasive ventilation *vs* 256, 551
  - hyperbaric 673, 785
  - idiopathic interstitial pneumonias 578
  - long-term *see* long-term oxygen therapy (LTOT)
  - nocturnal, Cheyne–Stokes respiration/central sleep apnoea 532
  - palliative 251
  - physiotherapist’s role 233
- ozone, air pollution 772, 773, 777

P
P2X3 receptor antagonist 112
paclitaxel chemotherapy, lung cancer 466
  NSCLC 229, 469
pain, chest *see* chest pain
pain management, palliative care 250
palliative care/treatment 249–252, 250
  COPD 330
  idiopathic pulmonary fibrosis 579
  implementation 249–252
  key processes 251
  lung cancer 463, 470
  physical support 250–251
  psychological support 251
  spiritual coaching 251
  terminal support 251
  timing, usage and patient deterioration interaction 249, 250
palpation 121
Pancoast's syndrome 456, 473
pancreas, cystic fibrosis-related disease 736, 737
pancreatitis, acute 730
'panda' sign 182
pandemic, definition 396, 397
pandemic influenza *see* influenza, pandemic
panel studies 757
panic attacks 250
Papanicolaou stain 7, 8
papillary hyperplasia 11
paprika splitter's lung 560
para-aminosalicylic acid (PAS) 423
para-bronchial structures 129
parallel studies 759
paraneoplastic effects, lung cancer 456
paraneoplastic syndromes
  lung cancer 456
  mediastinal tumours 515
  pulmonary carcinoid tumours 491
parapneumonic effusions 273–274, 275, 660
  causes 660
  complex 273–274
  management 664
  medical thoracoscopy/pleuroscopy 149
  simple 273, 274, 276
paraquat, metabolism 598
parasitic infections, cytological changes 12
para-tracheal structures 129
parenchymal lung disease, drug-induced 606–608
parenchymal nodules *see* pulmonary nodules
parenchymal pulmonary amyloidosis 593
parietal pleura 1
Particles in Exhaled Air (PExA) 190
particulate matter (PM), air pollution 772, 773, 777
patient-centred outcomes 753
patient information, pulmonary nodules 504–505
PD-1 227, 228
  antibodies/inhibitors 227, 228, 230
    NSCLC 469, 470
PD-L1
  antibodies/inhibitors 227, 228, 230, 467
    malignant pleural mesothelioma 512
    NSCLC 469, 470
    SBRT with, stage IV NSCLC 486
  predictive marker in lung cancer 230
  testing 15
  tumour cell expression 451, 467
PD-L2, tumour cell expression 451
peak expiratory flow (PEF)
  asthma 311, 312
    daily monitoring 312
    occupational asthma 750
  diurnal variability calculation 312
peak V'_{O_2} 71–72, 75, 461
peat moss worker's lung 560
PEComa 586
pectoralis major, congenital absence 121
pectus carinatum (PC) 649, 650
  indications for surgery 650
  surgical treatment 651
pectus excavatum (PE) 649, 650
  controversies 651
  indications for surgery 650
  surgical treatment 650–651
PEF *see* peak expiratory flow (PEF)
pembrolizumab 227, 228, 229, 467
  lung cancer 464
    NSCLC 467, 468, 469
pemetrexed chemotherapy
  lung cancer 466
    NSCLC 469
  malignant mesothelioma 470, 512
  pleural tumours 512
D-penicillamine, idiopathic interstitial pneumonias 576
pentamidine, *Pneumocystis* pneumonia 684, 685
peramivir, influenza treatment 395
percussion 122, 661
percutaneous drainage
  lung abscess 280
  see also chest tube drainage
percutaneous needle aspiration (PCNA) 209
performance status scales 464, 466
perfusion defects, detection
  angio-CT 182
  scintigraphy 181–182
perfusion (Q') lung scintigraphy (PLS)
  perfusion defects 181
  pulmonary embolism 181–182, 624, 625, 626
  sensitivity and specificity 181–182
pericardial effusion
  iatrogenic 603
  malignant 495–496
pericardial tuberculosis 435
pericarditis, tamponade due to 495–496
perifissural nodules 501–502
  malignant 503
periodic breathing, high-altitude 534, 779, 780

peripheral pulmonary lesions (PPLs), sampling techniques 208–209
peristalsis, oesophageal *see* oesophageal peristalsis
Perl's stain 10
peroral endoscopic myotomy (POEM) 702
peroxisome proliferator-activated receptor (PPAR)-γ 220
personalised medicine 187
personal protective equipment (PPE) 550
PET *see* positron emission tomography (PET)
PET/CT *see* positron emission tomography (PET)/CT
pH
    arterial 63
        acid–base disorders 63, 64
        determinants 63
        normal 63
    exhaled breath 190, 191
phagocytes, professional
    immunodeficiency 403, 404
        infections 675, 676
    see also macrophage(s); neutrophil(s)
phagocytosis, by alveolar macrophages, in COPD 24
pharmacokinetics, in lung tissues 598
pharmacotherapy, systemic 215–222
    cardiovascular drugs, impact on lung 216–220
    hypoglycaemic drugs, impact on lung 220–222
pharyngeal specimens, antigen tests 197
pharyngitis, group A streptococcal 375
phenic nerve stimulation 655
phosphodiesterase inhibitors
    PDE-4 inhibitors 347, 351
        see also roflumilast
    PDE-5 inhibitors, pulmonary arterial hypertension 634
    theophylline 347
phrenic nerve 5, 6
    lesions 658
    pacing 269
phrenic veins 6
physical activity
    assessment 246
    asthma and 310
    effect of pulmonary rehabilitation 241
    hospital admissions and 246
    in obesity 720, 721
    patient selection for pulmonary rehabilitation 246
    see also exercise
physical examination 117–123
    auscultation 123
    cough 118, 119
    dyspnoea 117, 118, 119
    inspection 120–121
    palpation 121
    percussion 122, 661
physiological dead space (V_D/V_T) 29
    ventilatory response during exercise 74
physiology *see* respiratory physiology
physiotherapists 232, 233
physiotherapy
    general principles 232–233
    respiratory *see* respiratory physiotherapy
Pickwickian syndrome 537
picture archiving and communication systems 158
(Pierre) Robin sequence 365
pigeon breeder's hypersensitivity pneumonitis 558, 560, 561
PIK3CA gene mutations 450–451
'pink puffers' 325
pirfenidone 182, 556, 576
    idiopathic pulmonary fibrosis 555, 576
Pisa score 620–621, 622
plasma cells, in lungs 22
platinum-based chemotherapy
    adverse effects 598
    NSCLC 469
        radiotherapy with 483–484
    SCLC 468
    see also carboplatin chemotherapy; cisplatin chemotherapy
platypnoea 647, 705
plazomicin 387
plethysmography, body 49–51, 87, 88
pleura
    anatomy 1
    drug-induced disease 609–610
    transthoracic ultrasound 162, 163
pleural adenocarcinoma, endoscopy 146
pleural adhesions 147
    chest ultrasonography before MT/P 146–147
pleural biopsy, closed percutaneous needle 510
pleural cavity 1
pleural disease
    asbestos-related 752
    in connective tissue diseases 724, 725
    transthoracic ultrasound 164–165
pleural effusion 660–665
    aetiology 660–661
        in a malignancy 495, 660–661
    chylous 586, 587, 588
    clinical presentations 661
    complex parapneumonic 273–274
    definition 660
    diagnosis, algorithm 662
    drug-induced 603
    empyema 274
    exudative 661
        assessment 135, 662, 663
        Light's criteria 663
        medical thoracoscopy/pleuroscopy 146, 149, 661
        pleural fluid analysis 663
    investigations/detection 661–662
        chest radiography 155, 275, 276, 295
        laboratory 662, 663
        medical thoracoscopy/pleuroscopy 146, 149, 661
        obligatory *vs* optional 663
        thoracentesis 151
        transthoracic ultrasound 163, 164, 165
        transudate *vs* exudate 663

  malignant *see* malignant pleural effusion (MPE)
  management 664
    interventional pulmonology 134–135
    thoracentesis (therapeutic) 151
  noncardiac 660
  one-sided, tuberculosis 434–435
  parapneumonic *see* parapneumonic effusions
  pathophysiology 661
  rate of onset 661
  recurrent
    management 135
    medical thoracoscopy/pleuroscopy for 146
  secondary 661
  simple parapneumonic 273, 274, 276
  systemic amyloid light chain amyloidosis 593
  transudative 661
  volume, classification by TUS 164
pleural fluid
  adenosine deaminase 664
  analysis 151, 152, 662, 663
    malignant pleural effusion 510
    obligatory *vs* optional parameters 663
    pleural infections 275, 664
  empyema 274
  exudative, medical thoracoscopy/pleuroscopy 149
  LDH 663
  normal production 661
  parapneumonic effusions 274
  total protein content 663
  in tuberculosis 434–435
  urinary antigen test applied to 197
  viscosity, drainage impairment 277
  volume 660
    classification by TUS 164
  volume required for analysis 152
pleural infection 273–278
  bacteriology 274, 275, 277
  clinical classification 274
  clinical presentation 273
  diagnosis 273, 664
  epidemiology 273
  imaging 275–276
  indwelling pleural catheter-related 278
  investigations 274–275
  management 276–277
  pathophysiology 273–274
  primary 274
  prognosis 277–278
  risk factors 273
  treatment 664
pleural malignancies *see* pleural metastases; pleural tumours
pleural metastases 495, 506, 507
  imaging 510
  malignant pleural effusions 507, 510
  prognosis 507–508
  transthoracic ultrasound 164–165
  treatment 511–512
  see also malignant pleural effusion (MPE)
pleural pain 108
pleural plaques, transthoracic ultrasound 165
pleural recesses 1
pleural rubs 123
pleural tap *see* thoracentesis
pleural tuberculosis 434–435
pleural tumours 507
  adenocarcinoma, endoscopy 146
  clinical signs 508–509
  diagnosis 508–511
  effusions *see* malignant pleural effusion (MPEs)
  malignant 506–507
  metastatic *see* pleural metastases
  primary *see* malignant pleural mesothelioma (MPM)
  staging 511
  treatment 511–512
pleurisy 507
pleuritis, tuberculous 435
pleurodesis 512
  chemical 664
  ipsilateral, lymphangioleiomyomatosis 588
  spontaneous, indwelling pleural catheter 513, 664
  surgical 512
  talc *see* talc pleurodesis
pleuropericardial cysts 515
pleuroscopy *see* medical thoracoscopy/pleuroscopy (MT/P)
plexiform lesion, pulmonary hypertension 630, 631
pneumococcal vaccination 381
  COPD patients 328, 336
  HIV-infected patients 683
  lymphangioleiomyomatosis 588
pneumoconiosis 750–751
Pneumocystis jirovecii, identification 12
Pneumocystis jirovecii pneumonia 390, 405, 408
  clinical features 684
  HIV-infected patients 683, 684
  imaging and molecular diagnosis 684
  mild, moderate or severe types 684
  outcome 685
  prophylaxis 685
    indications, and discontinuation 686
  treatment 684–685
pneumocytes, type II 9
  reactive changes 11
pneumocytomas 493–494
pneumomediastinum 669–670
  spontaneous 669
pneumonectomy
  disadvantages 475
  extrapleural, in mesothelioma 511
  *K*CO and *T*LCO 58
  lung cancer 475
    alternatives to 476–477
    survival after 473
  post-operative mortality 475
  pre-operative assessment 94
pneumonia 377–382
  in achalasia 702

  acute interstitial 297
  Aspergillus 391, 405, 407
  aspiration *see* aspiration pneumonia
  Candida 405, 407
  chemical pneumonitis leading to 412
  chemotherapy association 707, 708
  chest radiography 377, 378
  clinical features 378
  clinical stability, criteria 381, 382
  CMV 390
  community-acquired *see* community-acquired pneumonia (CAP)
  definition 377
  diagnosis and investigations 377, 378–379
    blood cultures 194, 196
    in haematological diseases 708
    ultrasound 167
    see also microbiological testing
  eosinophilic 599, 616–617
  epidemiology 377–378
  in haematological diseases 707–710
  hospital-acquired *see* hospital-acquired pneumonia (HAP)
  idiopathic interstitial *see* idiopathic interstitial pneumonias (IIPs)
  in immunocompromised hosts 378, 388–392
    Aspergillus 391, 405, 407
    Candida 405, 407
    CMV 390, 405, 406, 407
    diagnostic evaluation 389
    HIV-infected patients 390, 408, 683
    immediate antibiotic treatment 389
    management 381, 389
    Pneumocystis jirovecii 390, 405, 408
    in primary immunodeficiency 675
    tuberculosis 390, 408
    tuberculosis and HIV 390, 408
    see also immunocompromised hosts, opportunistic infections
  infiltrative
    acute respiratory failure 294, 296, 297
    chest radiography 295
  influenza complication 379, 394
  management 380–381
    noninvasive ventilation 549–550
  microbiology 379
  necrotising 296–297
  noninfectious, in haematological disease 710–714
  nosocomial *see* hospital-acquired pneumonia (HAP)
  in obesity 719
  organising *see* organising pneumonia
  Pneumocystis jirovecii see Pneumocystis jirovecii pneumonia
  post-operative 90
  post-transplant 406
  prevention 381
  primary viral 394
  severity assessment 379–380
  ventilator-associated *see* ventilator-associated pneumonia (VAP)
Pneumonia Severity Index (PSI) 379
pneumonitis
  acute, drug-induced 606
  cellular nonspecific 13
  chemical 412
  desquamative interstitial 13
  drug-induced 606
  giant cell 13
  in haematopoietic stem cell transplantation 709, 710
  HIV-associated 689
  hypersensitivity *see* hypersensitivity pneumonitis (HP)
  lymphocytic interstitial 13
  methotrexate 606
  radiation 487, 603, 612, 613
pneumopathy, acute lysis 711
pneumotachograph–shutter system, airway resistance measurement 49–50
pneumothorax 666–669
  catamenial 667
  causes 666
  chest radiography 295
    inspiratory–expiratory 157
  in cystic fibrosis 734
  definition 666
  epidemiology 666
  HIV association 689
  lymphangioleiomyomatosis 586, 588
  medical thoracoscopy/pleuroscopy 146, 147, 149
  post-endoscopic valve placement 284
  spontaneous *see* spontaneous pneumothorax
  tension *see* tension pneumothorax
  thoracentesis complication 153
  transthoracic ultrasound 166
poikilocapnia 44
point-of-care rapid antigen assays 687
Poland syndrome 649
poliomyelitis, sleep-related hypoventilation syndromes 538
pollution *see* air pollution
polyangiitis, granulomatosis with (GPA) *see* granulomatosis with polyangiitis (GPA)
polymerase chain reaction (PCR)
  real-time, drug resistant mycobacteria 205
  reverse-transcriptase (RT), influenza diagnosis 395
  tuberculosis diagnosis 420
polymeric lung volume reduction (PLVR) 285
polymyositis/dermatomyositis (PM/DM)
  clinical features 723, 725
  epidemiology 722
polysomnography 523, 531, 537
Pompe's disease 654
"popcorn" pattern, nodules 501
population attributable risk (PAR) 763, 764
posaconazole 391

- positive end-expiratory pressure (PEEP)
  - ARDS, ‘optimal’ 302
  - hypoxaemic respiratory failure 542
- positive expiratory pressure (PEP)
  - cystic fibrosis 235
  - primary ciliary dyskinesia 742
- positive predictive value (PPV) 767, 768
- positive pressure ventilators 267
- positron emission tomography (PET) 183
  - FDG-PET 183
    - indications 183
    - lung cancer 183, 456
    - malignant pleural effusions 510
    - pulmonary carcinoids 491
  - lung cancer 183, 456, 476
  - sarcoidosis 183
- positron emission tomography (PET)/CT 183
  - FDG-PET/CT
    - indications 183–184
    - lung cancer 183, 184, 457
    - lung cancer staging 460
    - pulmonary carcinoids 492
    - sarcoidosis 566
    - solitary pulmonary nodule 183–184, 455
  - mediastinal tumours 516–517, 518
  - pulmonary nodules 503–504
- positron-emitting isotopes 182–183
- posteroanterior (PA) radiograph 155, 156, 159
- post-expiratory pause 52
- post-inspiratory pause 52
- post-nasal drip syndrome 111
- post-operative interventions 93
- post-operative pulmonary complications
  - cardiac evaluation 92, 93
  - interventions to reduce risk 92, 93
  - intraoperative interventions 93
  - postoperative interventions 93
  - pre-operative assessment *see* pre-operative assessment
  - risk assessment 90
  - risk factors 90, 91
- post-splenectomy infection (OPSI) 409
- post-transplant complications *see* lung transplantation
- post-transplant obliterative bronchiolitis 413
- postural drainage (PD) 235, 280
- potassium ions 67
- Pott disease 436
- power (statistics) 763, 765
- PPAR-γ agonists 220
- prednisolone
  - asthma 348
  - drug-induced respiratory disease therapy 611
  - idiopathic interstitial pneumonias 574
  - idiopathic pulmonary fibrosis 556
- prednisone
  - idiopathic interstitial pneumonias 574
  - sarcoidosis 567
- pregnancy
  - air pollution effect 772
  - allergen immunotherapy (AIT) and 226
  - lymphangioleiomyomatosis 588
- pre-habilitation 90
- pre-operative assessment 90–96
  - cardiac evaluation 92, 93
  - pulmonary resection 94–95
- pre-operative interventions 92, 93, 94
- pre-operative risk, ASA classification 91
- pressurised metered-dose inhalers (pMDIs) 210, 211, 212
  - breath-actuated (BA-pMDI) 212, 213
  - with spacer 212, 213
- prevalence 756–757
- prevalence odds 756
- prevalence proportion 756, 757
- preventive fraction (PF) 763, 764
- primaquine, *Pneumocystis* pneumonia 684
- primary antibody deficiency (PAD) 675, 676
  - clinical presentation 679
  - interstitial lung disease in 677
  - respiratory diagnosis 679
  - spectrum of abnormalities 677, 678
- primary ciliary dyskinesia (PCD) 355, 740–743
  - clinical features 741, 742
  - diagnosis 355, 741–742
  - gene mutations 740, 742
  - athophysiology 740–741
  - treatment and follow-up 742–743
- primary immunodeficiency disorders (PID) 400, 675–680
  - antibody deficiency *see* primary antibody deficiency (PAD)
  - causes 675
  - classification 400–404
  - early diagnosis, importance 679
  - HRCT in 678
  - interstitial lung disease in 677, 678
  - malignancy risk 677–678
  - noninfectious respiratory diseases 676, 678
  - phagocyte disorders *see* phagocytes, professional
  - pulmonary infections 675
    - treatment 678–679
    - types 675, 676
  - spectrum of disorders 677, 678
- primary spontaneous pneumothorax *see* spontaneous pneumothorax
- primary tracheobronchial amyloidosis 360
- primary viral pneumonia 394
- probability 756
- programmed cell death protein 1 (PD-1) *see* PD-1
- programmed cell death protein ligand 1 (PD-L1) *see* PD-L1
- progressive massive fibrosis (PMF) 750, 751
- prone positioning
  - ARDS management 302
  - for CT 175
- prophylactic cranial irradiation, SCLC 468, 486
- *Propionibacterium acnes* 563
- Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study 620, 621, 623, 624

Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA–PED) study 620, 621, 624
prostanoids, in exhaled breath condensate 191
protein allergens 749, 750
proteinase-3 637
proteinase inhibitor (PI) deficiency *see* α_1-antitrypsin deficiency (AATD)
proteinosis, pulmonary alveolar *see* pulmonary alveolar proteinosis (PAP)
prothionamide therapy, pulmonary tuberculosis 423
proton therapy, NSCLC (stage III) 484
psammoma bodies 10
Pseudomonas aeruginosa infection
    after lung transplantation 406
    bronchiectasis 355, 356
    COPD exacerbation 334
    in cystic fibrosis 731, 732
    in haematological diseases 708
    hospital-acquired pneumonia 384, 386
    pneumonia, antibiotics for 381, 386
    in primary ciliary dyskinesia 743
    in primary immunodeficiency 675, 676
psoas abscess 436
psychological improvements, pulmonary rehabilitation 241
psychological support, palliative care 251
pulmonary alveolar proteinosis (PAP) 589–591
    auto-immune 589, 590
    congenital/hereditary 589
    epidemiology 590
    genetics 589
    natural history 590
    secondary 589
    treatment 590–591
    unclassified 590
pulmonary arterial hypertension (PAH) 628–629
    associated PAH, conditions 629–630
    causes 628, 629, 630
    in connective tissue diseases 723–724, 725
    diagnosis 631–634, 725
    exertional dyspnoea 104–105
    heritable, mutations 629
    HIV association 689
    idiopathic 628, 631
    pathobiology/pathology 630, 631
    risk assessment 631, 632
    survival/prognosis 630–631, 632
    treatment 634–636
        algorithm 634, 635
        in connective tissue diseases 725
        general measures 634
        newly diagnosed, initial therapy 634
        reassessment 634, 636
    types/classification 628–630, 629
pulmonary arterial pressure
    mean (mPAP) 628, 724
    radiation-induced lung injury 613
pulmonary arteries 4–5
    arteriovenous malformations *see* pulmonary arteriovenous malformations (PAVMs)
    bleeding, haemoptysis 298
    obstructions, pulmonary hypertension due to 629, 630
    in pulmonary hypertension 630
    remodelling 630
pulmonary arteriovenous malformations (PAVMs) 646–648
    aetiology 646
        see also hereditary haemorrhagic telangiectasia (HHT)
    clinical presentation 647
    definition 646
    diagnosis 647–648
    mutations associated 646, 647
    pathophysiology 647
    prevalence 646
    treatment 648
pulmonary artery wedge pressure (PAWP) 628, 724
pulmonary autonomic plexus 5
pulmonary barotrauma 783
pulmonary capillary haemangiomatosis (PCH) 630
    diagnosis 633
pulmonary capillary permeability, ARDS pathophysiology 300, 301
pulmonary capillary pressure, high-altitude pulmonary oedema 782
pulmonary-capillary transit time (tTR) 35
pulmonary carcinoids 490–493
    atypical intermediate-grade (AC) 490, 491, 493
    central and peripheral lesions 491
    clinical features 490
    diagnosis 491–492
    management 492–493
    paraneoplastic syndromes 491
    typical low-grade (TCs) 490, 491, 493
    WHO classification 490
pulmonary complications, post-operative *see* post-operative pulmonary complications
pulmonary congestion 530
pulmonary diffusive flux of oxygen 35
pulmonary disease *see* lung disease
pulmonary embolism (PE) 620–627
    acute respiratory failure in 294, 296, 298
    diagnostic strategies 620–626
        CT, dual-energy multislice spiral 170
        CT angiography 623–624, 624–625
        D-dimer measurement 621, 623
        in different clinical contexts 624–626
        general rules 621
        MRI 172–173
        perfusion (*Q'*) lung scanning 181–182, 624, 625, 626
        pre-test clinical probability 620–621
        scintigraphy guidelines 182, 624
        scoring systems for probability 620, 622
        ventilation (*V'*) scanning 182, 624
    follow-up, perfusion lung scintigraphy role 182
    in idiopathic interstitial pneumonias 577
    incidence 620
    isolated subsegmental 626

  pleural effusion secondary to 661
  recurrences, detection 182
  symptoms 620
pulmonary endarterectomy (PEA) 631, 636
pulmonary eosinophilic syndromes 616, 617
  drug-induced 616
pulmonary fibrosis
  in chronic hypersensitivity pneumonitis 559
  drug-induced 602, 608
  gastro-oesophageal reflux and 414
  idiopathic *see* idiopathic pulmonary fibrosis (IPF)
  in idiopathic interstitial pneumonias 569, 570
  in microscopic polyangiitis 642
  radiation-induced 488, 612, 613
pulmonary function tests
  adult pulmonary Langerhans cell histiocytosis 583
  asthma 312
    COPD *vs* 314–315
  drug-induced respiratory disease 603
  hypersensitivity pneumonitis 559
  interstitial lung disease in connective tissue diseases 724–725
  lung cancer 460–461
  lymphangioleiomyomatosis 586
  in obesity 717
  pre-operative 92
  pulmonary vasculitis 639
  rare airway diseases 359
  respiratory muscle weakness 654
  sarcoidosis 566
pulmonary gas exchange 34–39
  arterial blood gas analysis 60–69
  exercise testing 75
  failure, respiratory failure 541, 542
  impairment 34–37
    drug-induced 599
    see also hypoxaemia
  physiotherapy strategies to enhance 233
pulmonary haemorrhage, in haematological disease 710, 711
pulmonary hamartomas 493
pulmonary hypertension (PH) 628–636
  in adult pulmonary Langerhans cell histiocytosis 583
  chest pain 109
  chronic thromboembolic (CTEPH) 628, 629, 630, 631
    diagnosis 631, 633
    treatment 636
  classification/groups 628–630
    group 1 *see* pulmonary arterial hypertension (PAH)
    group 2 and group 3 629, 630
    group 4 629, 630
    group 5 629, 630
  definition 628, 720
  diagnosis 631–634
    algorithm 633
    perfusion lung scintigraphy 182
  drug-induced 599
  epidemiology 630–631
  high-altitude 782
  high altitude effect on pre-existing 782
  iatrogenic 610
  in idiopathic interstitial pneumonias 570
  in obesity 720
  pathobiology 630
  pathology 630
  post-capillary 628, 630
  pre-capillary 628, 630
  pulmonary diseases complicated by 693
  pulmonary rehabilitation 240
  radiation-induced 612
  referral to specialist centre 633
  in sarcoidosis 566
  survival/prognosis 630–631
  treatment 634–636
pulmonary infections *see* respiratory infections
pulmonary infiltrates and eosinophilia (PIE), drug-induced 606
pulmonary Kaposi sarcoma 688
pulmonary Langerhans cell histiocytosis, adult *see* Langerhans cell histiocytosis (LCH)
pulmonary lesions, in inflammatory bowel disease 701–702
pulmonary lobule 3
pulmonary metastases 496–498
  excavated 496, 497
pulmonary nodules 501–505
  adult pulmonary Langerhans cell histiocytosis 582
  assessment 501–502
  benign 501–502
  British Thoracic Society guidelines 501, 502, 503, 504, 505
  calcification 501
  cavitated 582, 641
  classification 501, 502
  in connective tissue diseases 724, 725
  criteria for discharge 501–502
  definition 501
  diagnosis
    CT for 501, 502, 505
    digital tomosynthesis 158
  Fleischner guidelines 501, 502, 503, 504, 505
  follow-up thresholds 502
  further investigations (PET/CT) 503–504
  granulomatosis with polyangiitis 641
  ground-glass (GGN) 455–456, 501, 502
    management 504
    see also ground-glass opacities (GGOs)
  health service implications 505
  malignancy predictors 504
  malignancy risk 502, 503
  measurement method 502, 505
  part-solid (PSN) 501, 502, 504
  patient information 504–505
  perifissural 501–502
    malignant 503
  prevalence 501
  small, associated with cysts 502, 503

  - smoking cessation and 505
  - ‘solid’ 501, 502
  - solitary 455–456
    - chest CT 184
    - follow-up 455
    - PET/CT and PET 183, 184
    - risk prediction model 455
  - sub-solid (SSN) 501, 502
    - management (invasive) 504
  - surveillance and referral 503
  - treatment 504
  - volume doubling time 503
  - volumetry 503, 505
- pulmonary oedema
  - acute, noninvasive ventilation 549
  - cardiogenic *see* cardiogenic pulmonary oedema
  - chest radiography 295
  - drug-induced 599, 603, 607
  - in haematological disease 711
  - high-altitude 781–782
  - immersion 785
  - noncardiogenic
    - after HSCT 714
    - drug-induced 607
- pulmonary perfusion scanning, lung cancer 461
- pulmonary plexus 3–4, 5
- pulmonary rehabilitation 239–248
  - aims and outcomes 239, 241, 243–244
  - in bronchiectasis 235
  - in chest wall disorders 236
  - choices for prescribing 242, 243
  - in COPD 240, 329, 336, 342
    - body composition changes, obesity 245
    - exacerbation 243, 246
    - exacerbation prevention 336
    - extrapulmonary consequences 244–245
    - patient selection for 244–246
    - pharmacological interventions with 245
    - physical activity levels 241
    - physiological improvement by 240
    - psychological improvement by 241
    - referral flow chart 244
    - symptoms 245–246
  - core elements of programme 239
  - definition 239, 243–244
  - evidence base 240–243
    - physical activity levels 241
    - physiological improvements 240
    - psychological improvements 241
    - utilisation of healthcare resources 242
  - ideal candidates 244
  - indications 239
  - integration into care plans 240
  - maintaining effects 243
  - in obesity 720–721
  - palliative care 251
  - patient selection 243–246
    - extrapulmonary effects of COPD 244–245
    - physical activity 246
    - severe exacerbations 246
    - symptoms 245–246
  - programme at home, and supervision 243
  - programme content 242–243
  - in pulmonary hypertension 240
  - referral, flow chart for 244
  - *see also* respiratory physiotherapy
- pulmonary rehabilitation team 239
- pulmonary–renal syndrome 638
- pulmonary resection
  - lung cancer *see under* lung cancer treatment
  - mortality 94
  - pre-operative assessment 94–95
  - *see also* lobectomy; pneumonectomy
- pulmonary sclerosing pneumocytoma 493–494
- pulmonary shunt, hypoxaemia due to 61, 62
- pulmonary surfactant *see* surfactant
- pulmonary tuberculosis (PTB) 416–428
  - aetiology 416–417
  - clinical features 419
  - diagnosis 419–421
    - gallium-67 scintigraphy 182
  - epidemiology 416, 418–419, 425
  - lifetime risk of developing 418
  - MDR-TB *see* multidrug-resistant tuberculosis (MDR-TB)
  - mortality 418–419
  - pathogenesis 417–418
  - prevention 426–427
  - primary 419
  - primary progressive 418
  - reactivation 418
  - secondary 419
  - treatment 421–426
    - drug dosages and side-effects 421, 422–424
    - duration 421
    - HIV infection with 421, 424
    - MDR-TB 424
    - sequelae after 426
    - *see also* anti-tuberculosis drugs
  - *see also* tuberculosis (TB)
- pulmonary vascular disorders (PVD)
  - exercise intolerance 70
  - exercise testing as prognostic indicator 75
  - oxygen pulse, exercise testing 72
  - pulmonary gas exchange impairment 75
  - *see also* specific disorders
- pulmonary vascular resistance (PVR), elevated 628
- pulmonary vasculitis 637–645
  - classification 638
  - clinical presentation 638
  - diagnosis 642
  - epidemiology 637–638
  - investigations 639
  - localised upper airway disease 644
  - pathogenesis 637–638
  - primary 638
  - prognosis 642
  - refractory, treatment 643–644
  - relapsing disease, treatment 643
  - secondary 638

    treatment 642–644
        induction phase 642–643
        maintenance phase 643
    see also eosinophilic granulomatosis with polyangiitis (EGPA); granulomatosis with polyangiitis (GPA); microscopic polyangiitis (MPA)
pulmonary vasculopathy, drug-induced 610
pulmonary vasodilators 782
pulmonary veins 3, 4, 5
    arteriovenous malformations *see* pulmonary arteriovenous malformations (PAVMs)
    in pulmonary hypertension 630
    stenosis, iatrogenic 603
pulmonary veno-occlusive disease (PVOD) 630
    diagnosis 633
    in haematological disease 714
pulmonology, interventional *see* interventional pulmonology
pump (respiratory) *see* respiratory pump
pure red cell aplasia 515, 516
pyrazinamide
    nontuberculous mycobacterial infections 445
    pulmonary tuberculosis 421, 422
    side-effects 422
    tuberculosis in immunocompromised patients 430
        HIV infection 686
pyroptosis 26
pyuria, aseptic 436

Q
quadriceps weakness 245
quality of life, predictor, dyspnoea 97

R
radial endobronchial ultrasound 130, 134
    lung cancer 456
radiation dose
    chest CT 170
    chest radiography 159
radiation fibrosis 612, 613
radiation-induced lung disease 612–614
    pathogenesis 612
    phases 612, 613
radiation-induced toxicity 487
radiation pneumonitis 487, 603, 612, 613
Radiation Therapy Oncology Group (RTOG) 483
radiobiology, tumour 482
radiofrequency ablation (RFA)
    airway obstruction 133
    lung cancer 472
radiofrequency (RF) pulse, MRI 172
radiography, chest *see* chest radiography
radiotherapy 612
    equipment, advances 481–482, 483
    five Rs 482
    lung cancer 481–489
        indications, by stage 487
    NSCLC stage II 483–484
    NSCLC stage III 483–484
    NSCLC stage IV 485
    palliative 470, 482, 486–487
    planning and doses 481, 483–486
    post-operative 484
    SCLC 468, 486
    techniques 482
    mechanism of action 482
    palliative 486–487
        lung cancer 470, 482, 486–487
    prophylactic, pleural metastases 512
    prophylactic cranial irradiation 468, 486
    side-effects 487–488, 598
        early/acute 487
        late/chronic 487–488
        lung disease due to 612–614
    stereotactic body *see* stereotactic body radiation therapy (SBRT)
    techniques 482
ramucirumab 467, 470
random errors 766
RANTES 25
rapid antigen tests 194, 195, 196–197
    pharyngeal specimens 197
    urinary 196–197
rapid eye movement (REM) sleep 536
    hypoventilation 536, 537, 539, 657, 719
RAPID score 278
rare airway diseases *see* airway diseases
Rasmussen's aneurysm 419
ratio, assessment of exposure–health outcome relationship 760, 761–763
    odds ratio 762–763
    risk ratio (for relative risk) 761–762
ratio scale 753, 754
Ravitch technique 650–651
Raynaud's phenomenon 724
reactive airways dysfunction syndrome (RADS) 748, 749, 750
reactive oxygen species 216, 777
rebreathing test 41, 43
recall bias 766
recanalisation of artery 648
RECIST criteria 512
recoil pressure (PREC) 32, 33, 48, 666
Reed–Sternberg cells 16
reflux *see* gastro-oesophageal reflux (GOR)
rehabilitation *see* pulmonary rehabilitation
relapsing polychondritis 361–362
relative risk (RR) 761, 763, 768–769
reliever medications, asthma 317, 344, 345
renal ammoniagenesis 66, 67
renal failure, amyloid A amyloidosis and 592
renal function tests, pulmonary vasculitis 639
renal tuberculosis 436
renal tubular acidosis 64
Rendu–Osler–Weber disease *see* hereditary haemorrhagic telangiectasia (HHT)
RENEW trial 285

- renin–angiotensin system 216, 217
- reserve cells 9
  - hyperplasia 11
- residual volume (RV) 83, 84, 85
  - age-related changes 85
  - asthma 312
  - decrease, restrictive diseases 85
  - emphysema/COPD 282
  - factors affecting 85
  - increase, obstructive lung diseases 85
  - measurement 87–88
  - in obesity 717
- resistance training 240, 243
- reslizumab 350
- respiration *see* breathing
- respiratory acidosis 63, 64
  - causes 65
- respiratory alkalosis 63, 64
  - causes 65
- respiratory bronchioles 3
- respiratory bronchiolitis-associated interstitial lung disease 143, 259, 569
  - *see also* idiopathic interstitial pneumonias (IIPs)
- respiratory compensation point (RCP) 72
- respiratory discomfort, during activity, dyspnoea 99
- respiratory distress, neonates 741
- respiratory effort 100
  - dyspnoea perceived as sense of 100
    - COPD 101
    - neuromuscular disorders 101–102
  - volitional, healthy subjects 98, 100
- respiratory emergencies 293–303
  - acute respiratory failure *see* acute respiratory failure (ARF)
  - ARDS 299–303
  - oxygen therapy 253
- respiratory epithelium
  - nonspecific reactive changes 10–14
  - papillary hyperplasia 11
- respiratory exchange ratio 29
- respiratory failure (RF) 541–552
  - acute *see* acute respiratory failure (ARF)
  - arterial blood gas analysis 60, 62
  - causes 541
  - chronic 538, 541
    - obesity hypoventilation syndrome 538
  - coexistence of types 542
  - definition 541
  - diagnosis 541
  - end-stage, in cystic fibrosis 734
  - hypercapnic *see* hypercapnic respiratory failure
  - hypoxaemic *see* hypoxaemic respiratory failure
  - neuromuscular diseases 653
  - pathophysiology 541, 542
  - postoperative, lung cancer 460
  - type 1 541, 542
    - *see also* hypoxaemic respiratory failure
  - type 2 542
    - *see also* hypercapnic respiratory failure
  - types 541, 542
  - in usual interstitial pneumonia (UIP) 570
- respiratory frequency (f_R) 29–30
- respiratory infections
  - bacterial *see* bacterial infections
  - bronchiectasis 355
  - cough due to 110
  - in cystic fibrosis *see* cystic fibrosis (CF)
  - cytology 11–12
  - diagnosis 194
    - *see also* microbiological testing
  - fungal *see* fungal infections
  - in haematological diseases 707–710
  - in HIV infection *see* HIV-related disease
  - in immunocompromised *see* immunocompromised hosts, opportunistic infections
  - lower tract *see* lower respiratory tract infections (LRTIs)
  - obesity and 719
  - pathogenesis 676
  - in primary ciliary dyskinesia 743
  - in primary immunodeficiency *see* primary immunodeficiency disorders (PID)
  - in pulmonary alveolar proteinosis 590
  - recurrent 675
    - cystic fibrosis 728, 730
    - microaspiration of gastric fluid 411–412
    - primary immunodeficiency 675, 676
  - smoking and 259
  - upper tract *see* upper respiratory tract infections (URTIs)
  - viral *see* respiratory virus infections
  - *see also* specific infections; specific pathogens
- respiratory mechanics 29–34, 48–53
  - COPD 32–33
  - expiration *see* expiration
  - inspiration *see* inspiration
  - measurement in mechanical ventilation 52
  - obesity hypoventilation syndrome 537
  - quiet breathing 48
  - restrictive lung disease 32
  - during sleep 536
- respiratory muscle(s) 48
  - dysfunction in connective tissue diseases 725
  - fatigue 32
  - REM sleep effect 536
  - training 234, 236, 237
    - in COPD 240
- respiratory muscle weakness
  - causes 653, 654
    - by pathology or speed of onset 654
  - investigations/evaluation 654–656
    - bedside tests 655
    - clinical evaluation 654–655
    - specialised tests 655–656
  - motor neurone disease/ALS 653–654
  - neuralgic amyotrophy 653
  - Pompe's disease 654
  - pre-existing/acquired 654
  - treatment assessment 656–658

respiratory-muscle work (W) 31–32
respiratory physiology 28–40
  dyspnoea and increase in ventilation 98, 100
  pulmonary gas exchange *see* pulmonary gas exchange
  respiratory mechanics *see* respiratory mechanics
  ventilatory requirements 28–29
respiratory physiotherapy 232–238
  airway clearance *see* airway clearance techniques
  disease-specific 233–238
    asthma 234
    bronchiectasis 234–235, 236
    chest wall disorders 236
    community-acquired pneumonia 236
    COPD 233–234
    critical illness 238
    cystic fibrosis 731
    dysfunctional breathing 234
    hyperventilation syndrome 234
    interstitial lung diseases 235–236
    lung abscess 280
    neuromuscular diseases 236–237, 658
    primary ciliary dyskinesia 742
    spinal cord injury 236–237
  general principles 232–233
  ventilation-/gas exchange-enhancing strategies 233
  see also pulmonary rehabilitation
respiratory pump 541
  failure 535
respiratory pump failure 535, 541, 542
respiratory quotient (RQ) 29
  reduced 34
respiratory sensitisers 749
respiratory syncytial virus (RSV)
  cytological changes 12
  diagnosis, nucleic acid amplification test 199
respiratory system
  amyloidosis localised to 593
  anatomy 1–6, 294, 541
  development 6
  resistance (R_{rs}) 51
respiratory tract infections *see* respiratory infections
respiratory virus infections
  acute bronchitis 320
  community-acquired, post-transplant 407
  COPD exacerbation 328, 333, 334
  COPD pathogenesis 22, 23, 25–26
  cytological changes 11
  diagnosis 195
    antigen tests on pharyngeal specimens 197
    nasopharyngeal aspirate 197
    nucleic acid amplification tests 198
    serological tests 198
  in haematological diseases 708
  in HIV infection 683
  in humoral immune deficiency 379
  hypersensitivity pneumonitis models and 558
  lower respiratory tract 199
  newly discovered 197, 198
  in primary immunodeficiency 675, 676
  upper respiratory tract 373, 375
restrictive allograft dysfunction (RAS) 291
restrictive lung disease
  functional residual capacity decrease 87
  respiratory mechanics 32
  sleep-related hypoventilation syndromes 536, 537–538
  see also specific diseases
RET gene rearrangements 450
reticular pattern 177, 498, 571
retinoic acid 710
retinoic acid syndrome 712
retropharyngeal space, infection spread 672
retrosternal pain 702
reverse-transcriptase (RT)-PCR, influenza diagnosis 395
Revised Cardiac Risk Index 92, 93
Reynolds number (R_e) 31
rheumatoid arthritis (RA) 362
  clinical features 723, 724, 725
  epidemiology 722
rhinitis
  allergic *see* allergic rhinitis/rhinoconjunctivitis (ARC)
  atrophic 360
  chronic, asthma association 315
  in eosinophilic granulomatosis with polyangiitis 638
  nonallergic 305
  occupational exposures 750
rhinoconjunctivitis, allergic *see* allergic rhinitis/rhinoconjunctivitis (ARC)
rhinosinusitis 373
  acute viral (common cold) 304, 372
  chronic *see* chronic rhinosinusitis (CRS)
rhinovirus 333, 683
Rhodococcus equi 11
Rho/ROCK 222
rib(s)
  fractures 164
  osteolytic metastases 499
  transthoracic ultrasound 162, 163, 164
rib suppression technique 158
rifabutin therapy, pulmonary tuberculosis 423
rifampicin
  latent tuberculosis 439
  nontuberculous mycobacterial infections 445
  pulmonary tuberculosis 421, 422, 424
  resistance to, detection 205, 686–687
  side-effects 422
  tuberculosis in immunocompromised patients 430
    HIV infection 686
rifamycins, pulmonary tuberculosis 424
  in HIV infection 686
rifapentine
  latent tuberculosis 439
  pulmonary tuberculosis 424
right heart catheterisation 633, 634, 723

right-to-left shunt 37, 648
right ventricular hypertrophy 612
rimantadine 395
riociguat 634, 636
ripasudil 222
risk 755–756
  differences between 763, 764
risk factors, measuring effects of exposure to 757–760
risk-modifying factors 759, 760
risk ratio 761
rituximab 408, 609
  pulmonary vasculitis 643, 644
(Pierre) Robin sequence 365
rociletinib 448
ROCK inhibitors 222
roflumilast 115, 329, 351
  COPD exacerbation management 115, 351
  COPD exacerbation prevention 337, 351
  side-effects 351
ROS1 gene rearrangements 450
Roughton–Forster equation 57
Rudakov technique 650, 651
rule of '130' 62

S

saddle nose deformity 362
salbutamol 345
saline, hypertonic, bronchial provocation test 81–82
salmeterol 345
sarcoid granulomas, cytological findings 12–13, 565
sarcoid-like granulomas 17
sarcoid-like reactions, drug-induced 608
sarcoidosis 362, 563–567
  acute 564
  aetiology 563
  airway manifestations 362
  cardiac involvement 566
  chronic 564
  clinical presentation 564
  definition 563
  diagnosis 564–566
    BAL findings 143, 145
    biopsy 565
    chest radiography 565–566
    endobronchial ultrasound 129, 130, 565
    gallium-67 scintigraphy 182
    HRCT 565–566
    initial evaluation 564
  diagnostic criteria 564
  differential diagnosis 182
    granulomatous-lymphocytic ILD 677
  epidemiology 563
  monitoring 567
  natural history 566, 567
  PET/CT 183
  prognosis 566
  pulmonary, treatment 567
  pulmonary hypertension 566
  sputum biomarkers 189
  treatment and follow-up 567
sarcoma, chest wall *see* chest wall, sarcomas
scales, measurement 753–754
  types 753, 754
scintigraphy
  chest pain investigation 109
  gallium-67 182–183
  perfusion lung *see* perfusion (Q') lung scintigraphy (PLS)
  pulmonary embolism diagnosis 624
  ventilation lung 182
sclerosing pneumocytoma 493
scoliosis
  hypoventilation syndromes 539
  ventilatory decompensation risk factors 268
scuba diving 784
seasonal influenza 393, 394
secondary spontaneous pneumothorax 666
  see also spontaneous pneumothorax
sedation, bronchoscopy 126, 128
segmental bronchi 3
segmentectomy, lung cancer 477
selection bias 766
self-management
  asthma 316
  behaviour modification 239, 240
seminoma 17
sense of effort, dyspnoea perception 100
sensitivity 767–768
serological tests 197–198
serotonin (5-HT), hypersecretion 491
serum amyloid A protein (SAA) 592
SERVE-HF trial 532
severe acute respiratory syndrome (SARS) 397–399
  clinical features 398
  diagnosis 398
    practice points 399
  epidemiology 397
  management 398–399
    noninvasive ventilation 550
  origin, phylogenetic studies 397, 398
  transmission and virology 397–398
severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) 397, 398
severe combined immunodeficiency (SCID) 401
severe congenital neutropenia (SCN) 403
short-acting β_2-agonists (SABA) 317, 345
  asthma 345
  COPD 329, 345
sildenafil 577, 634
'silent reflux' 412
silicone stents 133
silicosis 750–751
simulators, noninvasive ventilation (NIV) 551
simvastatin 342
single-breath technique, *T*LCO measurement 54–55
sinusitis
  asthma association 315
  bacterial, antibiotics for 375

sirolimus, in lymphangioleiomyomatosis 588
situs inversus 741
six-minute walk test (6MWT) 71, 245
Sjögren's syndrome (SS) 362–363, 593
  clinical features 725
  COPD in 724
  epidemiology 722
skeletal muscle dysfunction, COPD 244–245
  reversal, in rehabilitation programme 245
skeletal muscle fatigue 243
skeletal tuberculosis 436
sleep-disordered breathing (SDB) 523, 593
  see also sleep-related breathing disorders
sleep hypoventilation syndrome 268, 523
sleep-related breathing disorders 523, 535, 536
  central apnoea *see* central sleep apnoea
  Cheyne–Stokes breathing *see* Cheyne–Stokes respiration (CSR)
  diaphragm weakness 656–657
  drugs associated 610
  hypoventilation *see* hypoventilation syndromes
  neuromuscular diseases 657
  in obesity 719
  OSA *see* obstructive sleep apnoea (OSA)
  OSAHS *see* obstructive sleep apnoea–hypopnoea syndrome (OSAHS)
  in systemic amyloid light chain amyloidosis 593
sleep studies, neuromuscular disorders 657
small bowel, cystic fibrosis-related disease 736
small cell lung cancer (SCLC)
  cytology 14–15
  differential diagnosis 15
  extensive
    chemotherapy and radiotherapy 486
    survival and treatment 482
  limited
    radiotherapy 486
    survival and treatment 482
  prophylactic cranial irradiation 468, 486
  screening and 455
  staging 457
  survival, based on stage/treatment 482
  treatment
    chemotherapy 468
    first-line/second-line 468
    multimodal 468
    radiotherapy 468, 486
  see also lung cancer
smear, lung cytology 8
smear microscopy 202
smoke, carcinogens 453, 454
smokers
  identification 262
  lung cancer screening 454–455
smoker's cough 325
smoker's inclusion bodies 141
smoking 257
  associated diseases *see* smoking-related diseases
  BAL fluid, effects on 141
  CD8+ T-cells increase 21
  cessation *see* smoking cessation
  cigarette number smoked 263, 453–454
  COPD patients continuing 261, 263
  exposure, biomarker 264
  Heaviness of Smoking Index 263
  hypersensitivity pneumonitis protection 558
  leading preventable cause of death 257, 258
  maternal 258, 259
  necroptosis markers in bronchi 26
  pneumonia risk factor 381
  prevalence 257–258, 261
  pro-inflammatory effects 693
  second-hand (passive) 257, 259, 775
  third-hand 775
  T_{LCO} measurement and 57
smoking cessation 260, 261, 262
  5As approach 263, 264
  in adult pulmonary Langerhans cell histiocytosis 583, 584
  assisting patients 263
  in asthma 317
  benefits 454
  brief advice, efficacy 262
  in chronic bronchitis 321
  COPD management 263, 328
  high-intensity behavioural support and medication 262–263
  interventions 262, 263
  lung cancer screening increasing 455
  medication 263–264
  pulmonary nodule detection and 505
  relapse, dealing with 264
  symptoms during 261–262
  unwillingness 262
  Very Brief Advice (VBA) method 262, 328
smoking-related diseases 257–260
  acute eosinophilic pneumonia 616
  adult pulmonary Langerhans cell histiocytosis 581, 582
  asthma 259, 315
  cancer 259
  cardiovascular disease 259, 693
  chronic bronchitis 321
  chronic rhinosinusitis with nasal polyps 305–306
  COPD 20, 258, 261, 324, 340
    cardiovascular disease with 693
    in HIV infection 688–689
  epidemiology 257–258
  future challenges 259–260
  infectious diseases 259
  interstitial lung diseases 259
  lung cancer 259, 453–454, 755
    in HIV infection 688
  lung inflammation due to 325
  mortality 258
  pneumonia 381
  primary spontaneous pneumothorax 666
  pulmonary Langerhans cell histiocytosis 581, 582
  symptoms 258–259
sodium channel, epithelial (ENaC) 728

sodium ions 64, 65, 67
  loss, acid–base disorder 64, 65, 66
soft-mist inhalers (SMI) 211, 213–214
solid organ transplantation
  immunosuppression after 388, 389, 400
  nontuberculous mycobacterial infection 444
  opportunistic infections 389, 400, 405–408, 429
  see also lung transplantation
solitary pulmonary nodules *see* pulmonary nodules
somatostatin analogues (SS), in pulmonary carcinoids 492–493
somatostatin receptor scintigraphy, pulmonary carcinoids 491
specific immunotherapy *see* allergen immunotherapy (AIT)
specificity 765, 767–768
specimens
  cytology investigations 9
  exhaled breath analysis 190–191
  mycobacterial infection detection 202
  pharyngeal, antigen tests 197
  sputum, induced/induction 187
spinal cord compression 499
spinal cord injury (SCI)
  long-term ventilation 269
  radiation-induced 488
  respiratory physiotherapy 236–237
  sleep-related hypoventilation syndromes 538
spinal muscular atrophy
  respiratory failure 653
  type I, long-term ventilation 268–269
spine, tuberculosis 436
spiral CT *see* computed tomography (CT), spiral
spiritual coaching 251
spirometry
  asthma diagnosis 312
  bronchiectasis 354
  COPD diagnosis in heart disease 695, 697
  respiratory muscle weakness 654
  smoking cessation and 264
splenectomy, opportunistic infections after 409
split lung function, estimation 94, 95
spontaneous pneumomediastinum (SPM) 669, 670
spontaneous pneumothorax 666–669
  adult pulmonary Langerhans cell histiocytosis 582
  cannabis and 666–667
  causes and pathogenesis 667
  clinical features 667
  epidemiology 666
  imaging 667, 668
  medical thoracoscopy/pleuroscopy 149
  primary (PSP) 666, 667
  recurrent
    medical thoracoscopy/pleuroscopy 146
    prevention 669
  secondary (SSP) 666
  size 668
  small, management 669
  smoking and 666
  tension pneumothorax in 667
  treatment 667–669
    choosing 669
    lack of consensus 668
sputum 114–115
  in airway inflammation 188, 189, 322
  bloody *see* haemoptysis
  cell counts 188
  cultures 196
  in cystic fibrosis 189
  cytology 188–189, 196
  eosinophilia 188, 189, 615
    asthma 188, 189
    COPD 322
  Gram stain 196
  hypersecretion 114–115
    COPD 234
    management 114–115, 234
  inflammatory mediators 188, 189
  in lung abscess 280
  microbiological testing 196
  neutrophilia 188, 189
    COPD 188, 189, 322
  normal 188, 189
  production, acute bronchitis 320, 321
  pulmonary tuberculosis diagnosis 419–420
  purulent 114, 196
    bronchiectasis 353
    COPD exacerbation 334
  in sarcoidosis 189
  smear test, tuberculosis diagnosis 202, 419–420, 421
sputum, induced/induction 187–190
  asthma 314
  biomarkers for specific diseases 189
  cell counts, specific diseases 188–189
  indications/uses 187
  procedure 187, 420
  pulmonary tuberculosis diagnosis 420
  reproducibility and validity 190
  safety issues 188
  sample processing 187
squamous atypia 10
squamous cell carcinoma
  cytology 14
  keratinising or nonkeratinising 14
  molecular genetic abnormalities 448, 450, 451
  treatment 466
squamous cells 8, 10
  anucleate keratinised 10
  reactive 10
squamous dysplasia 14
squamous metaplasia 10
squeaks 123
staining techniques 7–8
stair climbing 92
  pre-operative assessment for lung resection 95
standardised uptake value (SUV) 183
staphylococcal infections, community-acquired pneumonia (CAP) 379

Staphylococcus aureus infection
    after lung transplantation 406
    aspiration pneumonia 412
    chronic rhinosinusitis 306
    cystic fibrosis 731, 732
    granulomatosis with polyangiitis (GPA) 638
    in HIV infection 683
    hospital-acquired pneumonia 384
    pneumonia complicating influenza 394
    primary ciliary dyskinesia 743
Starling resistor 523–524
STAT4 (signal transducer and activator of transcription) 21
static lung volume 83, 88
statins 217–218, 342
statistical interaction (effect modification) 766–767
statistical techniques 763, 769–770
stem cell(s) 579
stem cell-based therapy
    idiopathic interstitial pneumonias 579
    see also haematopoietic stem cell transplantation (HSCT)
stent(s)
    endobronchial 130
    types (silicone, metallic) 130, 133, 134
stenting, airway 130, 133, 134
STEP-IPF trial 577
stereotactic ablative radiotherapy, NSCLC stage II 484–485
stereotactic body radiation therapy (SBRT) 482, 484–485
    lung cancer
        early-stage 472, 485
        NSCLC stage II 484–485
        tumour location and size limit 485
    machines for 485
    side-effects 487, 488
        imaging pattern 603
STOP-BANG screening tool 92
STOP-TB strategy 426
streptococcal infections, group A 373, 375
Streptococcus
    hospital-acquired pneumonia 384
    pneumonia complicating influenza 394
    β-haemolytic, descending necrotising mediastinitis 672
Streptococcus pneumoniae infection
    aspiration pneumonia 412
    community-acquired pneumonia 379
    diagnostic approach 195
    in HIV infection 408, 683
    pneumonia complicating influenza 394
    primary ciliary dyskinesia 743
    in primary immunodeficiency 675, 676
    urinary antigen test 196
Streptococcus pyogenes, in primary immunodeficiency 675, 676
stridor
    infantile larynx (laryngomalacia) 367
    rare airway diseases 359
    subglottic stenosis 366
subcutaneous injection immunotherapy (SCIT) 224, 225
    side-effects 225–226
suberosis 560
subglottic stenosis 362, 366
    grading system 366
sublingual immunotherapy (SLIT) 224, 225
    side-effects 225–226
sulfonylureas 220
sulfur dioxide, air pollution 773
superior vena cava obstruction 120, 121, 456
superior vena cava syndrome 515
surfactant
    abnormalities, pulmonary alveolar proteinosis 589
    in alveolar macrophages 589
    clearance impairment 589
surfactant protein (SP)-B, and SP-C 589
surgeons, thoracic, qualifications 474
surgical therapy
    bronchiectasis 356
    chest wall disorders 650–651
    chronic rhinosinusitis 307
    complications *see* post-operative pulmonary complications
    COPD 329
    descending necrotising mediastinitis 673
    empyema 277
    lung abscess 280
    lung cancer *see* lung cancer treatment
    lung resection *see* pulmonary resection
    lung volume reduction *see* lung volume reduction surgery (LVRS)
    mediastinal tumours 518–519
    mesothelioma 511
    minimally invasive, lung cancer 477–478
    obstructive sleep apnoea–hypopnoea syndrome 527
    pre-operative assessment *see* pre-operative assessment
    pulmonary arteriovenous malformations 648
    pulmonary carcinoids 492
    spontaneous pneumothorax 669
    see also video-assisted thoracic surgery (VATS)
survival analysis 756
swallowing, impaired, aspiration due to 411
sweat chloride test 728, 729, 731
syndrome of inappropriate antidiuretic hormone 456
systematic errors 766
    see also bias
systemic lupus erythematosus (SLE)
    clinical features 723, 724, 725
    epidemiology 722
systemic pharmacotherapy, lung impact *see* pharmacotherapy, systemic
systemic sclerosis (SSc) 362–363
    clinical features 723, 725
    epidemiology 722
    nonspecific interstitial pneumonia 723, 724

T

- tadalafil 634
- talc pleurodesis 512, 664
  - criteria for 513
  - malignant pleural effusions 512, 513
- talc poudrage 135, 512, 664
  - medical thoracoscopy/pleuroscopy with 145, 149
  - spontaneous pneumothorax 669
- targeted lung denervation (TLD) 285
- targeted therapy
  - cystic fibrosis 735
  - NSCLC 464–467, 469, 470
- TBNA *see* transbronchial fine-needle aspiration (TBNA)
- T-cell(s) (T-lymphocytes)
  - blocking, in lung cancer 467
  - CD4$^+$ (helper) *see* CD4$^+$ T-cells
  - CD4/CD8 ratio in BAL fluid 143, 145
  - CD8$^+$ *see* CD8$^+$ T-cells
  - chronic airway inflammation 322
  - COPD 21, 22, 24
  - deficiency
    - HIV infection 429, 430
    - incidence, genes, and infections 401–402, 404
  - hypersensitivity pneumonitis 557, 558
  - immune checkpoint inhibitor action 467
  - *M. tuberculosis* infection 417, 418
  - response, to allergens 223
  - Th1 and Th2 cells, chronic airway inflammation 322
  - Th1/Tc1, in COPD 21
  - Th2 cells, asthma 322, 718
  - Th17 21, 23, 26
  - tolerance, allergen immunotherapy 224
- tedizolid 387
- telomeres, short, idiopathic pulmonary fibrosis 554
- temozolomide 492
- temperature, exhaled breath 191
- temporal subtraction, chest radiography 158
- tension pneumothorax 298, 667
  - acute respiratory failure 294, 296, 298
- teratoma, mature 515, 519
- terbutaline 345
- terizidone therapy, pulmonary tuberculosis 423
- terminal bronchioles 3
- terminal support 251
- tezacaftor 735
- theophylline 329, 347, 532
- thermoplasty, bronchial 131
- thiazolidinediones 220
- thin preparations, lung cytology 8
- thin-slice computed tomography *see* high-resolution computed tomography (HRCT)
- thioacetazone, pulmonary tuberculosis 423
- thoracentesis 151–153
  - complications 153
  - contraindications 153
  - diagnostic 151, 153
  - patient position 151
  - pleural effusion detection 661
  - procedure 152–153
  - set 151–152
  - therapeutic 153, 664
- thoracic duct 5
- thoracic lymph nodes 6
- thoracic oncologic surgery 474
- thoracic surgeons, qualifications 474
- thoracic surgery *see* surgical therapy
- thoracic ultrasound, pleural infections 274, 276
- thoracocentesis, malignant pleural effusions 510
- thoracoscopy
  - instruments 148
  - medical *see* medical thoracoscopy/pleuroscopy (MT/P)
  - pleural effusion cause 662
  - spontaneous pneumothorax 669
  - surgical 145
    - descending necrotising mediastinitis 673
    - malignant pleural effusions 511
    - *see also* video-assisted thoracic surgery (VATS)
- thoracotomy, descending necrotising mediastinitis 673
- thorax *see* chest
- thrombocytopenia 711
- thromboembolic disease, obesity as risk factor 720
- thrombus, pulmonary 623
- thymic carcinoma 518
  - cytology 17
- thymic cysts 515
- thymic epithelial tumours 518
  - TNM classification 518, 519
- thymic veins 5
- thymoma 515, 517
  - antibodies 518
  - cytology 17
  - histological diagnosis 518, 519
  - management 520
  - tumour markers 517–518
- thymus gland 5
- thyroid goitre 515
  - histological diagnosis 519
- thyroiditis, acute 374
- thyroid transcription factor (TTF-1) 14, 15, 448, 589
- tidal breathing protocol 79
- tidal volume (V_{T}) 29, 83, 84
  - changes, in voluntary increase in ventilation 101
  - constraints
    - in asthma 104
    - in interstitial lung disease 102, 103
  - exertional dyspnoea in COPD 101
- Tietze's syndrome 109
- Tiffeneau index 86, 325
- tigecycline 445
- tiotropium 346
- tissue plasminogen activator (tPA) 277, 664
- T_{LCO} *see* transfer factor of the lung for carbon monoxide (T_{LCO})
- tobacco
  - control measures 257–258

  heated tobacco products 260
  use, historical aspects 257
tobacco dependence 261–265
  physical, mental and social 262
  see also smoking
tobacco epidemic 257–258, 261
tobacco smoke
  composition 258
  exposure, biomarker 264
tobacco smoking *see* smoking
tolerable limit of exercise (T_{lim}) 73–74
tomosynthesis, digital 158
tonsillectomy 527
topotecan, SCLC 468
total lung capacity (TLC) 30, 83, 84
  asthma 312
  decrease, causes 85
  determinants 84
  increase, causes 84
  interstitial lung disease 102
  measurement 87–88
  in obesity 717
  T_{LCO} measurement and 54, 56
  usefulness 85
TP53 mutations 453
trachea
  anatomy 3, 358
  bronchoscopic assessment 127
  congenital anomalies 365, 367–370
  diameter 358
  dilatation 361
  nonspecific reactive changes 10
  obstruction, management 133
  position, determining 121
  rare diseases 358–363
  topographic anomalies 369–370
tracheal agenesis 367–368
tracheal atresia 367–368
tracheal bronchus ('pig bronchus') 369–370
tracheal cartilage calcification 362
tracheal stenosis
  congenital 369
  post-tracheostomy, stenting 134
tracheal wall 358
  weakness 368
tracheitis sicca 10
tracheobronchial amyloidosis 360, 593
tracheobronchial lesions, in inflammatory bowel disease 701–702
tracheobronchial nodules 360
tracheobronchitis
  chest pain 109
  in inflammatory bowel disease 702, 705
tracheobronchomegaly 361
tracheobronchopathia osteochondroplastica 360–361
tracheomalacia 368–369
  intrathoracic 368
tracheo-oesophageal fistula (TOF) 366, 368
  isolated (H-type fistula) 368
tracheostomy 267–268
  aims 268
  tracheal stenosis after, stenting 134
tracheostomy-delivered ventilation 266, 267, 268
  discharge planning 271
  indications 269
  in neuromuscular disease 269
  see also long-term ventilation (LTV)
tracheostomy tubes 267, 268
traffic-related air pollution 771, 772
tranexamic acid 298
transbronchial approach
  to central endobronchial lesions 208
  to peripheral pulmonary lesions 208–209
transbronchial cryobiopsy 130, 208
transbronchial fine-needle aspiration (TBNA) 128
  central airway lesions 208
  endobronchial ultrasound-guided 128, 129–130, 456–457
  hilar-mediastinal region lesions 209
  lung cancer 456
  peripheral pulmonary lesions 208
transbronchial lung biopsy 128, 130
  adult pulmonary Langerhans cell histiocytosis 583
  cryobiopsy 130, 208
  lung infection in immunocompromised hosts 389
  sarcoidosis 565
transdiaphragmatic pressure (PDI), measurement 655
transfer coefficient of the lung for carbon monoxide (K_{CO}) 56, 57
  physiological influences 57
  T_{LCO} relationship 57, 58
transfer factor of the lung for carbon monoxide (T_{LCO}; D_{LCO})
  calculation 55–57
  definition 54, 55–56
  idiopathic interstitial pneumonias 570
  idiopathic pulmonary fibrosis 554
  ILD in connective tissue diseases 724–725
  implications of $K_{\mathrm{CO}} \times V_{\mathrm{A}} = T_{\mathrm{LCO}}$ 57
  lung cancer 460
  measurement technique 54–55
  in obesity 717
  physiological influences 57
  reduced
    conditions with 554, 570
    neuromuscular diseases 654
  reference values, standardisation and guidelines 58
  use/benefits 54
transfer factor of the lung for nitric oxide (T_{LNO}) 57–58
  reference values, standardisation and guidelines 58
  uses/benefits 58
transfer factor of the lung for oxygen ($T_{\mathrm{LO_2}}$) 35–36
transfer factor of the membrane for carbon monoxide (T_{MCO}) 36
transforming growth factor-β (TGF-β) 23, 569, 647

transient receptor potential (TRP) 111, 113
    capsaicin-sensitive ‘hot’ (TRPV1) 111, 113
    TRPA1 111, 113
transmission electron microscopy 742
transplantation
    HSCT *see* haematopoietic stem cell transplantation (HSCT)
    lung *see* lung transplantation
    organ *see* solid organ transplantation
transpulmonary pressure (P_{tp}) 30
    hypoxaemic respiratory failure 542
transthoracic contrast echocardiography (TTCE) 647–648
transthoracic echocardiography
    pulmonary arteriovenous malformations 647–648
    pulmonary hypertension 631
trans-thoracic interventions 134
transthoracic lung biopsy, pulmonary nodules 503
transthoracic ultrasound (TUS) 160–168
    abnormal 163, 164–166
        chest wall disease 164
        pleural disease 164–165
        pleural effusion 163, 164, 165, 166
        pneumothorax 166
    advantages 160
    A-lines 162, 163
    artefacts 162
    B-lines 162, 163, 166
    image optimisation 162
    indications 160
    lung ultrasound 166–167
    normal 162, 163
    positioning for 161–162
    principles 160–161
    probes 160, 161
    technical aspects 161–162
    Z-lines (comet tails) 162, 163
treadmill exercise testing 71, 80, 81
tremelimumab 228
trimethoprim 684
trocars 148
TRP (transient receptor potential) channels 111, 113
tuberculin skin test (TST) 421
    extrapulmonary tuberculosis 434
    latent TB detection 439
    tuberculosis in immunocompromised hosts 431
tuberculoma 435
tuberculosis (TB) 201, 416–428
    aetiology 416–417
    arthritis 436
    CNS 434, 435–436, 687
    control programmes 421
    diagnosis and investigations 201, 419–421
        culture 203
        cytology, granulomatous reaction 11
        drug susceptibility testing 204–205, 390, 419, 420, 421
        in HIV infection 686–687
        identification of organism 203–204
        microscopy 202
        molecular detection 202–203, 686–687
        pleural fluid analysis 664
    drug-resistant
        detection 204, 205
        in HIV infection 686, 687
        molecular detection 205–206, 686–687
    epidemiology 416, 418–419, 425
    extensively drug-resistant *see* extensively drug-resistant TB (XDR-TB)
    extrapulmonary *see* extrapulmonary tuberculosis (EPTB)
    gastrointestinal 436
    genitourinary 436
    global elimination goal 427
    as global emergency 416
    HIV co-infection 390, 408, 419, 433, 685–686
        antiretroviral therapy effect 443, 687, 689–690
        countries with high burden 425
        drug-resistance 686, 687
        epidemiology 419, 431, 685
        extrapulmonary TB 419, 686
        immune reconstitution disease 443, 687, 689–690
        immunodeficiency 429
        molecular diagnostic assays 686–687
        number needed to treat 431
        presentation and diagnosis 686
        pulmonary TB 685–686
        response to treatment 687
        treatment 421, 424, 430, 686
    in immunocompromised patients 390, 419, 429–432
        clinical presentation 430
        delayed diagnosis 430
        development after latent TB 438–439
        diagnosis 430, 433, 439
        incidence and risk 429, 431
        latent TB screening 439–440
        mortality 430, 431
        pathomechanisms 429–430
        prevention 430–431
        treatment 430
    lasting immune response 438
    latent *see* latent tuberculosis infection (LTBI)
    lymphadenitis 434
    meningitis 434, 435
    miliary 435
    multidrug-resistant (MDR) *see* multidrug-resistant tuberculosis (MDR-TB)
    ocular 437
    pericardial 435
    pleural 434–435
    prevention 426–427
    pulmonary *see* pulmonary tuberculosis (PTB)
    reactivation 430, 434
    at risk, diagnosis 426
    skeletal 436
    subclinical, in HIV infection 687, 690

  treatment 390
    first-line drugs 204, 205
    second-line drugs 204
  'unmasking', immune reconstitution disease 443, 690
  as UN priority 426
  vaccine 427
Tuberculosis Network European Trials group (TBnet) 431
tuberous sclerosis complex (TSC) 585, 586
  management 588
tumour(s)
  after lung transplantation 291
  chest wall *see* chest wall tumours
  in HIV infection 688
  lung *see* lung cancer; lung tumours
  mediastinal *see* mediastinal tumours
  metastatic *see* metastatic tumours
  pleural *see* pleural metastases; pleural tumours
  tumour cells
  elimination, immune response 451
  immune tolerance 467
  immunoediting response 451
  PD-L1 and PD-L2 expression 451, 467
tumour mutational burden, as predictive marker 230
tumour necrosis factor (TNF)-α
  antibodies/antagonists 408, 577
    increased TB associated 430
  ARDS pathophysiology 301
  in COPD 340
  in idiopathic pulmonary fibrosis 577
tumour radiobiology 482
turbulent flow 31
type I error (error α) 763
type II error (error β) 763, 765
type II pneumocytes 9
  hyperplasia 11
tyrosine kinase inhibitors (TKIs) 447, 465
  EGFR 448, 465
    resistance mechanisms 448–449, 465
    side-effects 465
  haematological disease, complications 712
  idiopathic interstitial pneumonias 577
  resistance to 448–449, 465
  see also specific drugs

U
ulcerative colitis 705
ultrasound
  B-mode (brightness mode) 161
  chest 146–147
  in pneumonia 378
  deep vein thrombosis 625
  diaphragm function 656
  Doppler 161
  endobronchial *see* endobronchial ultrasound (EBUS)
  endoscopic (EUS) 129–130
  lung 166–167
  M-mode (motion mode) 161
  pleural diseases 135
  spontaneous pneumothorax 667
  thoracic, pleural infections 274, 276
  transbronchial fine-needle aspiration with 208
  transthoracic *see* transthoracic ultrasound (TUS)
ultrasound probes 161
ultrasound waves 160–161
ultrathin bronchoscope (UTB), lung cancer 456
umeclidinium 346
upper airway
  acute obstruction 294, 295, 296
  angio-oedema, drug-induced 598
  malformations 364–365
  nasal CPAP and 526
upper airway collapse, obstructive sleep apnoea 522, 523, 719
  pathophysiology 523–524
upper airway disease 304–307
  in cystic fibrosis 737
  in pulmonary vasculitis 644
upper respiratory tract infections (URTIs) 372–376
  complications 373–374
  diagnosis 374
  differential diagnosis 374
  pathogens 373
  predisposing conditions 373
  prevalence 372
  prevention 375
  signs and symptoms 373
  spectrum of 372
  transmission 372
  treatment 375
  viral
    cough 110
    influenza *see* influenza
    transmission and patterns 110
  see also respiratory infections
urinary antigen tests 196–197
usual interstitial pneumonia (UIP)
  biopsy, guidelines against 572
  chest HRCT 554, 570, 571
    idiopathic pulmonary fibrosis 554, 555
  'definite' pattern 555
  'indeterminate' pattern 555, 570, 571
  inflammatory–fibrotic process 569
  'probable' pattern 555
  prognosis 570
uvulopalatopharyngoplasty, obstructive sleep apnoea 526, 527

V
V'_{A} *see* alveolar ventilation (V'_{A})
vaccination
  in COPD 328, 336
  influenza *see* influenza, vaccination
  pneumococcal *see* pneumococcal vaccination
VACTERL association 367, 368
vagal afferent nerves, hypersensitivity 110

- vagus nerve 5
- valganiciclovir 407
- valves
  - endobronchial 131, 135, 283
  - intrabronchial 283
  - placement *via* bronchoscope 283–284
- varenicline 263, 264
- variability (random error) 766
- variable, definition 753
- vascular endothelial growth factor (VEGF)
  - inhibitors 588
  - pulmonary arteriovenous malformations 647
- vascular endothelial growth factor (VEGF)-D 586, 587
- vascular remodelling, radiation-induced 612
- vasculitis
  - ANCA-mediated 297, 637
  - necrotising 640
  - pulmonary *see* pulmonary vasculitis
  - recurrent haemoptysis 115
  - systemic 638
- vasodilation, hepatopulmonary syndrome 704
- vasodilators, pulmonary 782
- vasopressin 64, 65, 67
- $V'\text{CO}_2$ (carbon dioxide output) 28, 72–73, 75
- $V'\text{E}$ (minute ventilation) 28, 29, 41–47
  - carbon dioxide responsiveness 41, 42–44, 46
  - exercise challenge test and 80
  - hypoxia responsiveness 42, 44–46
  - increase, exercise testing 74
  - $V'\text{CO}_2$ relationship, ventilatory efficiency 72–73
  - $V'\text{E}$-$P\text{ETCO}_2$ relationship 41, 42, 43, 44
  - voluntary increase in ventilation, physiology 100
- vehicular exhausts, pollution 772, 774
- venous drainage
  - diaphragm 6
  - lungs 4–5
  - pleura 1
  - trachea 3
- ventilation 48
  - control 41–47
    - response to hypoxia 44–46
    - response to inhaled CO_2 42–44
    - *see also* $V'\text{E}$ (minute ventilation)
  - high-intensity, COPD 270
  - in hypercapnic respiratory failure 253
  - long-term *see* long-term ventilation (LTV)
  - mechanical *see* mechanical ventilation
  - noninvasive *see* noninvasive ventilation (NIV)
  - in obesity 717
  - physiotherapy strategies to enhance 233
  - response to exercise 74
  - $V'\text{E}$-$P\text{ETCO}_2$ relationship 41, 42, 43, 44
- ventilation (V') lung scintigraphy (VLS) 182, 624
- ventilation–perfusion (V'/Q') mismatch 38–39
  - acute exacerbation of COPD 544
  - arterial blood gas analysis 61
  - hepatopulmonary syndrome 704
  - hypoxaemia due to 61, 62
  - normal lung 38
  - pulmonary embolism diagnosis 624
  - pulmonary hypertension 631
- ventilator(s)
  - ‘intelligent’ 549
  - long-term ventilation 267
  - noninvasive ventilation 547, 548, 549
- ventilator-associated pneumonia (VAP) 383, 384
  - definition 383
  - mortality 385, 386
  - risk factors 385
  - treatment 386–387
- ventilator care plan 267
- ventilatory decompensation, risk factors in scoliosis 268
- ventilatory drive, disorders 266
  - sleep-related hypoventilation 535
- ventilatory efficiency 72–73
- ventilatory failure 541, 542
- ventilatory limitation 74, 83–84
- ventilatory recruitment threshold 43–44
- ventilatory requirements 28–29
- Venturi mask 253
- vertebral metastases 499
- Very Brief Advice (VBA) method 262
- video-assisted thoracic surgery (VATS) 145
  - idiopathic interstitial pneumonias 572
  - lung cancer 477
  - spontaneous pneumothorax 669
- videobronchoscope 127
  - flexible 124, 125
- vilanterol 345
- vinblastine 584
- vinorelbine chemotherapy, lung cancer 466
  - NSCLC 469
- virus infections *see* respiratory virus infections
- visceral pleura 1
- visual analogue scale (VAS), dyspnoea 100
- vital capacity (VC) 85–86
  - asthma 312
  - diaphragm weakness 654
  - expiratory (EVC) 86
  - high altitude 780
  - increase, volume response 87
  - inspiratory (IVC) 86
- *VKORC1* allele 604
- $V'\text{O}_2$ (oxygen uptake) 28, 29
- vocal cords, bronchoscopic assessment 126–127
- vocal fremitus 121
- vocal resonance 123
- volatile organic compounds (VOCs), air pollution 774
  - indoor 775, 776
- volume-assured ventilation modes 267
- volumetry, pulmonary nodules 503, 505
- vomiting, metabolic alkalosis 67
- voriconazole 391, 407
- V'/Q' *see* ventilation–perfusion (V'/Q') mismatch
- $V\text{T}$ *see* tidal volume ($V\text{T}$)

W

walking tests 71, 245
wandering opacities, drug-induced respiratory disease 602
washings, bronchial 127, 208
weight loss
  cystic fibrosis 731
  obesity hypoventilation syndrome 538
  obesity management 720
  obstructive sleep apnoea improvement 721
Wells score 620, 621, 622
wheezing 123
  asthma 297, 310
  lung congestion 297
whispering pectoriloquy 123
whole-body plethysmography 49–50, 51
whole-genome sequencing, *M. tuberculosis* complex 205–206
whole-lung lavage (WLL) 590, 591
whooping cough 373, 375
  see also Bordetella pertussis
Williams-Campbell syndrome 361
wind instruments, hypersensitivity pneumonitis 560
Wiskott-Aldrich syndrome 401
wood pulp worker's lung 560
wood trimmer's disease 560
work-exacerbated asthma (WEA) 748, 749
  see also occupational asthma
work-related asthma (WRA) 748–750
  epidemiology and types 748, 749
  see also occupational asthma
World Health Organization (WHO)
  COPD, common cause of death 324
  End-TB strategy 426
  obesity definition 716
  STOP-TB strategy 426
  tobacco control 257, 258
  tuberculosis treatment 421
World Health Organization (WHO)/Eastern Cooperative Oncology Group scale 464, 466

X

XpertMTB/RIF assay 205, 687
Xpert Ultra assay 205
X-ray, chest *see* chest radiography

Y

yolk sac tumour 17

Z

zafirlukast 349, 350
zanamivir
  influenza prophylaxis 395
  influenza treatment 395
Ziehl–Neelsen stain 7, 11, 202, 417, 419–420
Z-lines, transthoracic ultrasound 162, 163
Z protein 744, 745